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Original Articles

VARIATIONS IN EGG WHITE AND EGG YOLK COMPONENTS OF VIRUS AND RICKETTSIAL VACCINES

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INTRODUCTION

THE occurrence of untoward reactions following immunization procedures with virus and rickettsial vaccines has been well documented. Evidence for the role of hypersensitivity factors in many of these instances has been included in a comprehensive review of the subject by Untracht and Ratner.[1] The fact that many species of viruses and rickettsiae require culturing in the developing chick embryo, its amniotic and allantoic fluid, or its yolk sac may result in the incorporation of inseparable egg proteins during vaccine production.[2-3] This has usually been a source of concern to those considering the administration of such vaccines to known egg-allergic patients.[4-5] However, wide degrees of variation in tolerance to these vaccines have been exhibited by egg-sensitive persons, and an unpredictable reactive clinical response to immunization is often noted. Questions arising from such observations have led to this study, which is concerned with a qualitative antigenic analysis of common virus and rickettsial vaccines for chicken egg white and egg yolk components.

MATERIALS AND METHODS

Precipitin Tests.—The antigenic reactivity of virus and rickettsial vaccines for egg components was studied through their participating role in the formation of in vitro antigen-antibody precipitates. An attempt was made to resolve each preparation into constituent egg white and egg yolk fractions

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by employing the vaccine as a test antigen in precipitin tests with rabbit antisera to chicken egg white and to egg yolk in gel media. Patterns of reaction in agar-filled Petri dishes, according to the double diffusion technique of Ouchterlony,[6] were thus noted for each of the following commercially available preparations:

(1) *Virus vaccines:* Polyvalent influenza virus (Eli Lilly, Lederle, Merck Sharp & Dohme, Parke Davis, Pitman-Moore), mumps (Lederle), yellow fever (National Drug), smallpox (Lederle), rabies (Squibb), lymphogranuloma venereum skin test antigen (Lederle), all of chick embryo origin, and rabies (Eli Lilly) prepared in the duck embryo.

(2) *Rickettsial vaccines of chick embryo origin:* Rocky Mountain spotted fever (Lederle) and typhus, epidemic type (Lederle).

Each band of precipitate formed within the agar was verified as a true antigen-antibody reaction by the development of coalescence with one similar band resulting from the adjacent reactions of egg white–anti-egg white or egg yolk–anti-egg yolk systems. Further identification of the antigenic component of the immune precipitate was attempted by searching for similar reactions of identity with some egg white fractions (for example, crystallized ovalbumin, lysozyme, ferric complex of conalbumin, and reference antisera) or by noting a characteristic location for the precipitin band in agar according to the immunologic patterns described by Kaminski.[7]

Antiserum to Egg White.—Rabbits were immunized with whole egg white carefully aspirated through a hole placed in the shell of a chicken egg. Each animal received a total of 12 ml. of egg white given in twelve equally divided doses of saline-diluted material over a three-week period. The first four injections were given intravenously, the next four by alternating intraperitoneal and intravenous routes, and the last four subcutaneously. Antiserum was prepared from whole blood obtained by cardiac puncture seven days following the last injection. Individual antisera, subsequently pooled, were demonstrated to contain antibody components to seven to ten distinct egg white fractions, of which one or two could also be detected in egg yolk. There is an obvious disparity in the number of egg white fractions determined by different techniques, such as detection by antigen-antibody reactions and the employment of physicochemical methods responsible for the isolation of ovalbumin, conalbumin, ovomucoid, lysozyme, globulin, ovomucin, and avidin. These differences may possibly be explained by the demonstration, with immunologic techniques, of the presence of an unidentified antigenic impurity in ovalbumin,[9] the heterogenicity of ovomucoid,[10] the multiplicity of albumin and globulin fractions, the inconstant immunochemical behavior of lysozyme in gels, and the lack of antigenicity of avidin.[7]

Antiserum to Egg Yolk.—Egg yolk was prepared by separating the intact yolk from the white of a chicken egg, carefully rolling the intact yolk on filter paper to remove adsorbent white particles, washing the intact yolk

in running water for one hour, and carefully dissecting away a small portion of the yolk sac to allow aspiration of the yolk through a needle and syringe. Rabbits were immunized with a total dose of 12 ml. of egg yolk given in twelve equally divided doses of saline-diluted material over a three-week period. One milliliter was given on each of four days of every week. All injections were given intravenously except those on the first day of the second and third weeks, which were given intraperitoneally. Individual antisera, subsequently pooled, were demonstrated to contain antibody components to seven or eight distinct constituents of egg yolk, of which at least one or two could be detected in egg white. Egg yolk was also prepared by freezing the whole chicken egg and thawing carefully removed pieces of the frozen intact yolk which could be easily separated from the frozen white without contamination. Precipitin tests with both types of yolk preparations and the rabbit antisera to egg yolk exhibited identical patterns. Chemical methods have demonstrated that egg yolk proteins consist of six fractions (lipovitellin, livetin, lipovitellenin, phosvitin, vitellin, vitellenin).[9] The immunochemical properties of egg yolk constituents have not been characterized, however, and the antigen-antibody precipitate bands noted in gel could not be identified.

RESULTS

The results of precipitin tests recorded for each virus and rickettsial vaccine with antisera to egg white and to egg yolk as the diffusing reactants in agar gel are shown in Table I.

TABLE I

VACCINES	NUMBER OF PRECIPITIN BANDS	
	ANTISERUM TO EGG WHITE	ANTISERUM TO EGG YOLK
Mumps	1	1
Rabies (duck)	4	3
Yellow fever	5	3
Rabies	7	6
Small pox	8	7
Influenza polyvalent		
Brand A	5	6
Brand B	0	0
Brand C	7	4
Brand D	0	0
Brand E	5	4
Lymphogranuloma venereum	2	1
Rocky Mountain spotted fever	3	3
Typhus (epidemic)	1	4

The patterns of these precipitate bands representing qualitatively distinct antigen-antibody systems is diagrammatically represented in Fig. 1. These demonstrated a marked variation in the egg white and egg yolk component reactions for each vaccine.

COMMENT

In the immunization of rabbits with either egg white or egg yolk, it was found impossible to obtain an antiserum that did not possess at least one or

two common antibody components. Extreme care was taken in separatory techniques in order to avoid criticism directed to an impure, white-contaminated yolk antigen. The precipitin patterns noted in agar gel would thus tend to confirm the suspicion of a common sensitizing antigen to egg white and egg yolk reported on the basis of Schultz-Dale techniques[2b, 11] and studies

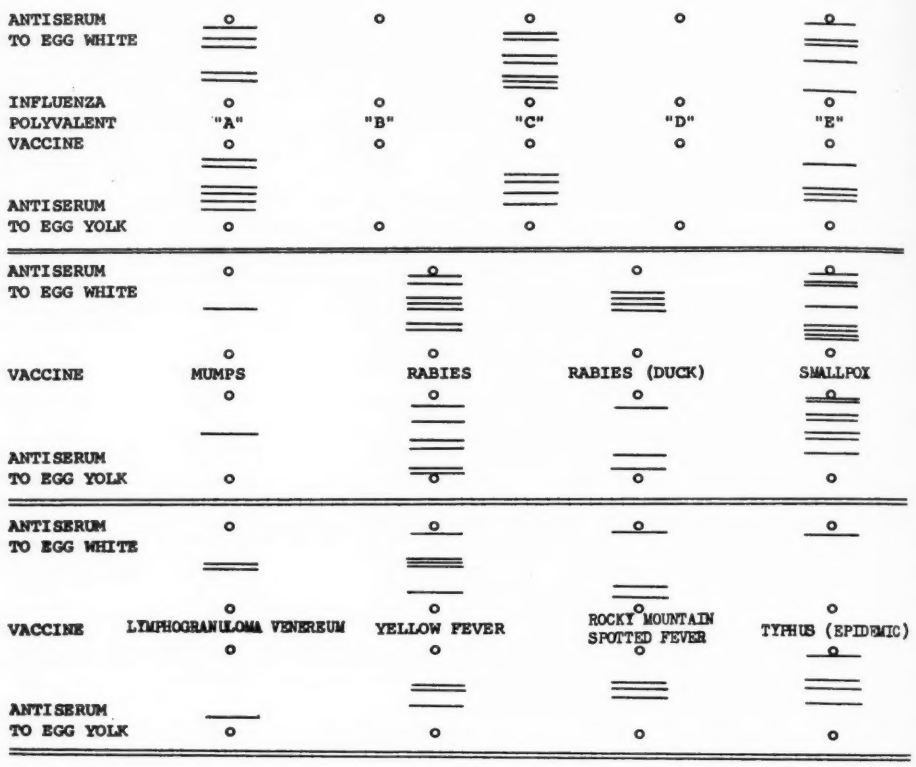

Fig. 1.—Diagrammatic representation of results of precipitin tests by the double diffusion technique (Ouchterlony) utilizing virus and rickettsial vaccines of egg embryo origin and antisera to egg white and to egg yolk as reactants. Each transverse line represents a distinct band of antigen-antibody precipitate placed in its relative position noted within the agar.

employing passive transfer of serum reagins.[11] Onoe[12] was able to isolate ovomucoid from egg yolk, while Marshall and Deutsch,[13] utilizing immunologic techniques, reported the presence of conalbumin and a trace of ovalbumin in yolk. Because of our inability to obtain a chemically pure recrystallized ovalbumin fraction, it was impossible to identify absolutely this antigen, common to egg white and egg yolk, by immunologic reactions of identity. However, the precipitin band patterns in gel suggested characteristics for ovalbumin and/or conalbumin.

The detection of antigenic fractions of chicken egg white and egg yolk in rabies vaccine of duck embryo origin emphasizes the need for caution in attempting to delineate clinical allergy to virus vaccines on the basis of species

origin of the egg culture. Such cross-reactivity for many components of egg whites of other fowl with those of chicken has been recorded in serologic studies.[14]

Neither components of either egg white or egg yolk could be detected by specific antisera in two lots of polyvalent influenza virus vaccine. When apprised of this finding, the manufacturers were unable to offer any reasonable explanation. One did suggest, however, that the presence of an incorporated phosphate carrier might possibly be a factor, inasmuch as protein might be adsorbed to the carrier with a resultant decrease in its reactivity.

The marked variation in content of antigenic egg white and egg yolk fractions within the virus and rickettsial vaccines studied is evident when their precipitin reaction patterns are compared with common antisera. This qualitative variation existed in different lots of influenza virus vaccines, even when presumably prepared by similar methods of egg inoculation, harvesting, concentration, and purification. Reasons for this are not apparent. No evident correlation was noted between any particular egg white or egg yolk component of the vaccine and that portion of the egg (allantoic fluid, whole embryo, yolk sac) utilized in the culture of the virus or rickettsial microorganism in question.

In evaluating hypersensitivity reactions to virus and rickettsial vaccines, consideration must be given to the biologic effects and properties of the inoculated microorganisms themselves.[1] Another important factor might well be a quantitative one relating the amount of constituent egg proteins of a vaccine to the degree of clinical sensitivity of an egg-allergic recipient. This has not been a subject of study in this report. However, it has been noted that qualitative differences may exist in the reaginic antibodies of egg-sensitive man.[1c] Therefore, the results of this study would suggest that one important determinant of allergic reactivity or any vaccine may be the variable presence of that particular protein fraction of egg white and/or egg yolk for which the recipient possesses clinical sensitivity.

SUMMARY

1. Rabbit antisera to chicken egg white and to egg yolk demonstrated common antibody constituents by double diffusion precipitin studies in agar gel with the Ouchterlony technique. Because of impurities in the egg white fractions, the antigen common to egg white and egg yolk could not be definitely identified as ovalbumin and/or conalbumin.

2. These antisera were employed in similar precipitin test procedures to detect qualitative egg white and egg yolk components of some virus and rickettsial vaccines of chick and duck embryo origin.

3. A wide variation in the number and types of component egg white and egg yolk fractions was found to exist among the vaccines.

4. It is suggested that one determinant of allergic reactivity for a vaccine requiring chick embryo culture in its preparation might be the variable

presence of that particular protein fraction of egg white and/or yolk for which the recipient may possess clinical sensitivity.

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THE OCCURRENCE OF ALLERGIC DISEASE IN PATIENTS WITH CUSHING'S SYNDROME

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THE concept of a relationship between adrenal cortical function and hypersensitivity reactions rests on studies linking these areas which have been recorded over many years.[1-3] More recently, extensive investigation of adrenal steroids and of adrenal corticotrophic hormone has been possible with observations of their effects on both naturally occurring allergic states and on experimentally induced hypersensitive states.[4, 5] That adrenal cortical steroids can influence allergic diseases has been well demonstrated. The clinical course of hay fever and of bronchial asthma has been measurably influenced by therapeutically administered cortisone.[6-8] The administration of ACTH, which induces secretion of endogenous adrenal cortical hormones, also favorably affects the allergic state.[9, 10]

Prednisone and prednisolone have been found to have comparable influences on the course of allergic diseases in therapeutic doses approximately one-fourth to one-fifth the effective dose of cortisone.[11, 12]

Additional steroid compounds differing in minor molecular configuration from cortisone are currently under investigation. Certain of these (for example, 9α-fluorohydrocortisone) have a greater influence on salt and water metabolism; others exhibit anti-inflammatory properties which appear to be correlated with effects on allergic states. Methylated derivatives of prednisolone and triamcinolone are being evaluated with respect to their influence on allergic diseases.[13, 14]

MATERIAL

We have studied the occurrence of allergic disease in a group of patients with Cushing's syndrome, which is primarily a disorder resulting from excessive secretion of cortisone-like hormones of the adrenal cortex. A series of 101 patients with this condition was studied at the Mayo Clinic. In each case unequivocal clinical evidence, and usually laboratory evidence as well, confirmed a diagnosis of Cushing's syndrome. Nineteen patients were observed to have tumors arising from the adrenal cortex, and eighty-two were found to have hyperplasia involving the adrenal cortex.[15] Five tumors were malignant and fourteen were benign adenomas. All patients were treated by either subtotal or total adrenalectomy.

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We have either examined and queried each patient concerning allergic diseases or reviewed his history for references to allergic disease in an effort to determine whether or not an association exists between the allergic state and Cushing's syndrome.

In those patients in whom Cushing's syndrome has developed, adrenal function has progressed from a state in which it was normal to one in which an excessive secretion of adrenal steroid has been manifest. After both total and subtotal adrenalectomy these patients have invariably been regarded as having potential or actual adrenal cortical insufficiency, and those undergoing total adrenalectomy have required maintenance doses of steroid preparations. After resection of a hyperfunctioning adrenal tumor, the remnant of adrenal cortex has been observed to be relatively hypoactive over periods of weeks to months, presumably as a consequence of the high preoperative titer of circulating adrenal corticosteroids.

RESULTS

We have found eight patients who presented allergic manifestations associated with Cushing's syndrome (Table I). Six of these had allergic reactions following the use of various drugs; the other two patients had bronchial asthma and allergic rhinitis which antedated the onset of Cushing's disease and which were present at the time that early manifestations of Cushing's syndrome developed.

TABLE I. THE OCCURRENCE OF ALLERGIC DISEASE IN PATIENTS WITH CUSHING'S SYNDROME

PATIENT	ALLERGIC MANIFESTATION	DRUG ANTIGEN	STATUS OF CUSHING'S SYNDROME AT TIME OF ALLERGIC REACTIONS	
			BEFORE OPERATION	AFTER OPERATION
1	Bronchial asthma; hay fever		See Fig. 1	See Fig. 1
2	Bronchial asthma; vasomotor rhinitis		See Fig. 2	See Fig. 2
3	Maculopapular drug rash	Potassium thiocyanate	Reaction	
4	Urticaria	Penicillin	Reaction	No reaction while receiving 50 to 200 mg. cortisone daily
5	Maculopapular drug rash	Dihydrostreptomycin		Reaction after first stage (no cortisone); no reaction after second stage (50 to 100 mg. cortisone daily)
6	Urticaria	Tetanus antitoxin; penicillin	Reaction	
7	Bullous dermatitis	Potassium iodide		Reaction while receiving 30 mg. of cortisone daily
8	Drug rash	Gantrisin		Reaction

Among those patients presenting drug allergy, sensitivity to several drugs was observed. The drugs included penicillin, dihydrostreptomycin, tetanus antitoxin, Gantrisin (3,4-dimethyl-5-sulfanilamido-isoxazole), potassium iodide, and potassium thiocyanate.

Patients with nasal allergy and bronchial asthma have been observed to experience changes in the severity of these diseases with the occurrence of Cushing's syndrome. Striking remissions of nasal allergic disorders and bronchial asthma were correlated with the development of Cushing's syndrome. With surgical extirpation of a major part of the functioning adrenal cortex, allergic symptoms recurred. A less clear-cut relationship was observed concerning drug allergy among patients with Cushing's syndrome. Reports of the eight cases follow.

CASE REPORTS

Case 1.—A 16-year-old white girl presented herself at the Mayo Clinic on March 6, 1950. She related a history and presented findings of Cushing's syndrome then of eighteen months' duration.

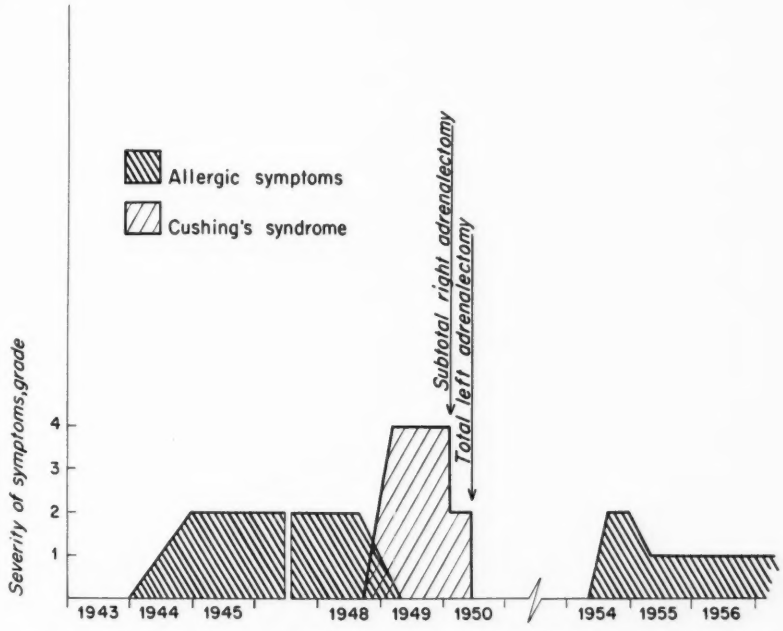

Fig. 1.—Allergic disease in Cushing's syndrome. Summary of data in Case 1.

On April 3, 1950, subtotal right adrenalectomy was performed and 6.5 grams, an estimated 90 per cent, of the adrenal gland was removed. The patient's convalescence following this operation was uneventful.

On June 24, 1950, exploration of the remnant of the right adrenal gland showed viable adrenal cortical tissue. Left total adrenalectomy was then done. The left adrenal gland weighed 11.6 grams and revealed cortical hyperplasia. Again, an uneventful convalescence followed operation. Although adrenal cortical extract was used during the early postoperative period, no maintenance program of steroid drug therapy was employed subsequently.

Three months after the second operative procedure there had been a striking remission in the manifestation of Cushing's syndrome.

The patient had a strongly positive family history of allergic disease. Her father had experienced eczema and asthma. An older sister was subject to eczema. A first cousin on the maternal side was asthmatic, as was a paternal uncle.

When the patient was 10 years of age, seasonal hay fever with both seasonal and perennial asthma had developed. She would experience exacerbations of asthma several times each year, usually following upper respiratory infections.

Six months after the insidious beginnings of Cushing's disease all allergic symptoms disappeared and were not manifested again during the period when Cushing's syndrome was present or for four years after its surgical correction; asthma then recurred. Asthma again developed after a severe upper respiratory infection and at a time when the patient was seven months pregnant. Subcutaneous injections of Adrenalin hydrochloride were required for symptomatic relief. Periodically since 1954 asthma has occurred in a mild form, particularly following respiratory infections, exertion, and breathing of cold air. The patient's seasonal hay fever recurred in 1956 (Fig. 1).

Case 2.—A 26-year-old white woman first presented herself at the clinic in 1940 with a history of asthma, then of five months' duration. It had occurred in the winter months and was associated with vasomotor rhinitis. An allergy survey revealed positive skin

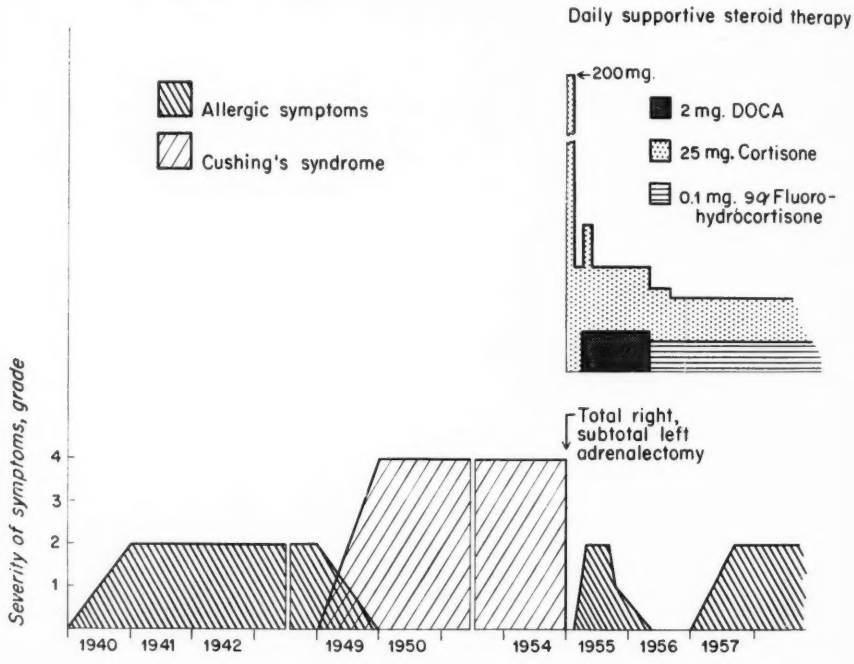

Fig. 2.—Allergic disease in Cushing's syndrome. Summary of data in Case 2.

reactions to dog and cattle hair, house dust, feathers, and certain ingestants. No other significant disease was observed in the course of studies on that occasion. Despite antiallergic measures, the patient continued to have frequent exacerbations of bronchial asthma and vasomotor rhinitis, largely during the winter months.

In 1949, early symptoms of Cushing's syndrome developed. It is of considerable interest that with the onset of Cushing's syndrome the patient became entirely free from

bronchial asthma and vasomotor rhinitis and remained free for five years. At this time (December, 1954) she again came to the clinic and striking changes associated with Cushing's syndrome were apparent. On Jan. 3, 1955, the patient underwent total right adrenalectomy and subtotal left adrenalectomy. Her postoperative convalescence proved uneventful. Supportive measures included injections of cortisone in the early postoperative period and, later, 30 mg. daily of cortisone administered orally. For a short period in February, 1955, because of nausea, the daily dose of cortisone had been increased to 50 mg. with 2 mg. of Cortate being added to the regimen.

Progressive remission in symptoms and signs of Cushing's syndrome followed the surgical procedure (Fig. 2). Despite maintenance steroid therapy during the early postoperative course, however, a recurrence of moderately severe asthma developed within two months after surgical intervention. The asthma was of approximately the same degree of severity as that experienced prior to the onset of symptoms of Cushing's syndrome. It occurred in attacks requiring both ephedrine and injections of Adrenalin in oil for relief from nightly attacks.

The patient returned for postoperative evaluation of her Cushing's syndrome in April, 1955. An allergy survey undertaken to test her reaction to common inhalant allergens (miscellaneous substances, grasses, pollens, weeds, and molds prevalent in her community) revealed entirely negative skin reactions. A program of antiasthmatic measures was outlined in detail. These included precautions to avoid common inhalant allergens, abstinence from smoking, and measures to control bronchitis.

The patient was again seen in July, 1955, at which time asthma persisted and she still required continuing medication for symptomatic relief. In October, 1955, she was having less asthma and required relatively little medication for its control. On subsequent visits in July and November, 1956, the patient was having virtually no trouble with asthma and required no medication for its relief. The asthma recurred, however, in October, 1957. Its pattern was similar to that experienced prior to the onset of Cushing's syndrome.

In the management of Cushing's syndrome she was ultimately able to effect a further reduction in maintenance steroid therapy, until she required only 15 mg. daily of cortisone and 0.1 mg. of 9α-fluorohydrocortisone daily.

Case 3.—A 51-year-old white woman presented herself at the clinic on Aug. 25, 1945. She was observed to have classic Cushing's syndrome.

In June, 1945, 3 grains of potassium thiocyanate three times daily for four days of each week had been prescribed. After 2 months a maculopapular rash had developed over a wide portion of her back. She had discontinued the medication one week before she was seen at the clinic. The rash was already subsiding. She was seen in consultation in the Section of Dermatology, where she was considered to have dermatitis medicamentosa resulting from the use of potassium thiocyanate. The concentration of cyanate in the blood had not been determined during the period when she had used the drug.

The patient underwent right adrenalectomy on Nov. 9, 1945, and partial left adrenalectomy on Jan. 26, 1946. At the time of the first operation the skin reaction had subsided, and it posed no problem then or later in the course of the patient's management.

Case 4.—A 47-year-old white woman presented herself at the clinic on Sept. 19, 1953. She related a history of urticaria that had developed after oral ingestion of penicillin tablets one month prior to the time of examination. Clinically the patient was observed to have symptoms of Cushing's syndrome. These had been present for at least four years. Urticaria was not present at the time of her examination at the Mayo Clinic.

Right adrenalectomy was done on Oct. 6, 1953, and a cortical adenoma that measured 3 by 3 by 2 cm. was removed. The patient's postoperative course was complicated by right pleural effusion which on two occasions necessitated thoracentesis. It was of interest that during two periods totaling seventeen days in the postoperative phase of her care, the patient received penicillin by injection and on a third occasion she received penicillin by aerosol.

Urticaria from penicillin did not develop during the postoperative period. During periods when penicillin was administered and tolerated, however, the patient was receiving cortisone orally in daily doses ranging from 50 to 200 mg.

Case 5.—A 23-year-old white woman presented herself at the clinic in November, 1951, with Cushing's disease then of ten years' duration.

On Dec. 4, 1951, the patient underwent left subtotal adrenalectomy and right total adrenalectomy. Small nodules were encountered in both adrenal glands. These were considered to be "nonfunctioning" adenomas.

The patient's convalescence proved uneventful, aside from a maculopapular eruption which developed ten days after operation, spreading diffusely over much of the body within four days. It was thought to result from the injection of dihydrostreptomycin. With discontinuation of the use of this medication, the rash faded and disappeared within several days. Cortisone was not being administered when the rash appeared.

The patient returned in November, 1953, relating a history of initial regression in all symptoms of Cushing's syndrome. In the six months prior to her readmission, however, the symptoms of Cushing's syndrome had recurred. The remnant of the left adrenal gland was removed. During the postoperative period the patient was given one brief course of dihydrostreptomycin by injection without any evidence of intolerance. At the same time she was also receiving supportive doses of cortisone intramuscularly in doses ranging from 50 to 200 mg. daily.

Case 6.—A 44-year-old white woman first presented herself at the clinic in January, 1951. She had symptoms of Cushing's syndrome which had developed insidiously, beginning three years prior to her registration. Two-stage bilateral adrenalectomy was performed.

One year prior to her registration at the clinic, at a time when Cushing's syndrome was already established, tetanus had developed. Tetanus antitoxin was administered, as was penicillin. An urticarial reaction had occurred after the administration of these medications employed in the management of tetanus. The reaction had abated, however, and was no problem at the time the patient registered at the clinic.

Case 7.—A 43-year-old white woman presented herself at the clinic in September, 1950. She related the history of an illness of six months' duration. A diagnosis of Cushing's syndrome was made. The patient declined exploration of the adrenal glands, however, and no definitive treatment was undertaken.

She returned for further consideration on Jan. 28, 1952. On Feb. 19, 1952, bilateral total adrenalectomy was performed, after which the symptoms of Cushing's disease regressed. Bronchitis developed, however, as a sequel to an upper respiratory infection approximately two and one-half years later. An iodide expectorant was administered. In two days large, clear blebs developed on the skin; these were considered to be a manifestation of bullous dermatitis medicamentosa resulting from the use of iodides. With cessation of medication with iodides, the reaction promptly subsided. At that time the patient was being maintained on 30 mg. daily of cortisone.

Case 8.—A 20-year-old white woman was admitted to the clinic on June 14, 1954, with classic Cushing's syndrome. Symptoms were then of two years' duration.

On June 24, 1954, an adrenal cortical adenoma was removed with part of the left adrenal gland. The patient's convalescence proved essentially uneventful. In the course of her postoperative care, however, Gantrisin was administered because of a low-grade urinary tract infection. Following the use of this drug for two days (July 20 and 21), a skin rash developed which abated after discontinuation of the medication. The patient was not receiving any maintenance steroid therapy at the time the rash appeared.

COMMENT

The effect of adrenal cortical hormones on the hypersensitive state has been well established. It would appear that adrenal cortical compounds having

an "anti-inflammatory" activity are more effective in influencing the hypersensitive state than are substances directed primarily toward salt-and-water metabolism. The dosage of these hormones required to influence the hypersensitive state differs considerably. Steroids elaborated by the adrenal cortex are known to undergo many changes in the course of their intermediary metabolism, particularly within the liver. Individual variations in the intermediary metabolism of these substances may well exist. Disease processes may alter the pattern of these intermediary processes, thereby leading to an altered steroid structure. Perhaps the basis for the so-called allergic diathesis may lie within such congenital or acquired metabolic defects.

As yet, studies of the adrenal cortex have been concerned primarily with the quantitative aspect of adrenal cortical function. A consideration of qualitative changes as induced by various disease entities on hormones elaborated by the adrenal cortex is less well understood. Additional information may be derived from further study of patients having adrenal disease, by further study of altered steroid metabolism induced by other disease processes, and through further chemical separation or synthesis of steroid compounds. As the steroid preparations become available, their functions are being reviewed for possible influences on the allergic state.

It would appear quite possible that, as yet, we remain on the periphery of the problem of adrenal cortical disease and its relationship to the ephemeral "allergic state." It is possible that those adrenal cortical steroids already tested are effective only generally and not as specifically as other still unknown substances. Through studies correlating adrenal and allergic disease, the adrenal facet of the allergic state may be defined further.

SUMMARY AND CONCLUSIONS

At the Mayo Clinic eight of 101 patients with Cushing's syndrome were found to have histories or findings of allergic diseases. Among the patients having Cushing's syndrome were nineteen who had hyperfunctioning tumors of the adrenal cortex; five of the tumors were malignant. The remainder of the patients presented adrenal cortical hyperplasia. Of the eight patients presenting histories of allergic disease, six had experienced untoward reactions following the use of medications. Two patients presented histories of asthma and hay fever. An analysis of the course of the allergic disease during periods of relatively normal, increased, and decreased adrenal cortical function has been made.

It would appear that drug allergy may occur in patients manifesting either excessive or deficient adrenal cortical function. The occurrence of drug allergy was insufficiently frequent to warrant conclusions as to the possible effect of adrenal cortical functions on its course. Allergic reactions occurred both before and after the surgical correction of Cushing's syndrome by extirpation of the adrenal glands. However, large doses of cortisone administered during postoperative care effectively suppressed drug allergy when drugs which had previously elicited allergic reactions were given.

In patients having nasal allergy and bronchial asthma a study was made concerning the severity of allergic symptoms during periods of relatively normal, excessive, and deficient adrenal cortical function. These states existed prior to the onset of Cushing's syndrome, during the time the disease was active, and after the surgical removal of all or part of both adrenal glands or of adrenal cortical tumors. It would appear, from a review of the cases of two patients concerning whom extensive data were available, that the allergic state is ameliorated at times when Cushing's syndrome is active. Conversely, it would appear that surgical treatment for Cushing's syndrome by extirpation of much or all of the functioning adrenal cortical tissue is followed by a return of symptoms arising from allergic disease.

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EXPERIMENTAL DEPLETION OF MONONUCLEAR CELLS FOR THE PURPOSE OF INVESTIGATING REACTIONS OF THE ALLERGIC CONTACT TYPE

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WITH THE TECHNICAL ASSISTANCE OF SONYA STROYMAN

INTRODUCTION

THE significance of the mononuclear cells in allergic contact dermatitis of guinea pigs is examined in this study. The contact type of sensitivity in guinea pigs can be transferred to normal animals only by a sufficient number of viable mononuclear cells withdrawn from the lymphatic system or the blood system of sensitized animals.[1] Furthermore, chemical,[2, 3] histopathologic,[4] and histochemical[5] studies of contact dermatitis of guinea pigs indicate that the capacities of the mononuclear leukocytes induced through sensitization are largely responsible for the allergic response. Humphrey[6] employed a rabbit antiserum against guinea pig polymorphonuclear cells to study the development of the Arthus phenomenon. Inderbitzin[7] used rabbit antiserum against guinea pig mononuclear cells and succeeded in inhibiting the tuberculin reaction. He also investigated the effect of this antiserum on the allergic contact reaction but noted no change in the degree of sensitivity. The publications cited have sparse data on the immunologic properties of these rabbit antisera or on the changes in the blood following their administration and do not record control experiments with normal rabbit serum to establish the effect of the injection of a foreign protein.

For this study a rabbit anti-guinea pig mononuclear cell serum was produced; its immunologic properties were examined, the blood changes after intravenous administration were established, and simultaneously the effect of the induced blood changes on allergic contact dermatitis was determined. Control experiments using normal rabbit serum were made in order to establish the unspecific effects of a foreign protein.

MATERIALS AND METHODS

Antigen.—The mesenteric lymph nodes of exsanguinated male albino guinea pigs were cleaned of fat and connective tissue. The nodes were deep-frozen and cut into small pieces. Several grams were placed in a Pyrex glass bottle with glass beads and shaken with 20 ml. of 0.85 per cent saline for forty-eight

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TABLE I. COMPARATIVE STUDY OF THE IMMUNOLOGIC PROPERTIES OF RABBIT ANTI-GUINEA PIG MONONUCLEAR CELL SERUM AND NORMAL RABBIT SERUM*

		HEMOLYSIS†	HEMAGGLUTINATION†	PRECIPITATION‡		SKIN REACTION§	
				LYMPH NODE ANTIGEN	SERUM	IMMEDIATE	ARTHUS
Fresh antiserum		+(1/50)		++	++	+++	+
Fresh normal serum		+(1/10)		–	–	–	–
Heated antiserum		–	+(1/25)	+	+	+++	+
Heated normal serum		–	–	–	–	–	–
Heated antiserum	Incubated with guinea pig erythrocytes	–	–	+	+	+++	+
Heated normal serum		–	–	–	–	–	–
Heated antiserum	Incubated with guinea pig erythrocytes and serum	–	–	–	–	+-	–
Heated normal serum		–	–	–	–	–	–

*Each test evaluation represents an average of two to four experiments.

†Serum dilutions in 0.85 per cent saline were used for hemolysis and hemagglutination tests. Washed guinea pig erythrocytes (0.05 ml. per test tube) were used as antigen. The tubes were kept at room temperature and examined several times within eight hours.

‡The precipitation technique described as agar gel diffusion[10] was used. Estimates of precipitin content were made on a comparative basis.

§Rabbit sera, 0.1 ml. and rabbit and guinea pig sera mixture, 0.2 ml., were injected intradermally to normal male albino guinea pigs. Intensity of the skin response was graded as follows: erythema (+), induration (++), and central hemorrhage (+++). If the reaction progressed to necrosis, it was recorded forty-eight hours later as a positive Arthus phenomenon.

hours. The yield, a milky suspension, was used for sensitizing injections. A clear filtrate of this suspension was used as the antigen for precipitation of the antiserum.

Sensitization.—Male New Zealand albino rabbits, weighing 2,500 grams each, were injected intramuscularly with 1 to 2 ml. of the antigen suspension. Six injections were made in one month. With the first two injections, made within the first week, equal amounts of Freund's adjuvant* were administered. The rabbits were bled seven days after the last antigen injection and the sera were pooled.

Antiserum.—The pooled antiserum was heated at 57° C. for one hour. Next, a one-fourth volume of washed guinea pig erythrocytes was added. The mixture, kept at room temperature for twelve hours, was stirred frequently and then centrifuged at 3,000 r.p.m. for thirty minutes. The supernatant serum was mixed with an equal volume of normal guinea pig serum; forty-eight hours later the precipitins were removed by centrifugation at 3,000 r.p.m. for two hours. *This mixture of rabbit antiserum to guinea pig mononuclear cells and normal guinea pig serum (referred to as anti-MC serum) was used to induce depletion of the mononuclear cells in the guinea pigs.* After each step of the procedure just described, a sample of the antiserum was kept for immunologic examination. Results of the immunologic tests are given in Table I and contrasted with the results of identical tests using normal rabbit serum, processed in the same way as the anti-MC serum.

Heating of the serum and its incubation with guinea pig erythrocytes destroyed its hemolyzing and hemagglutinating activities, respectively. The addition of normal guinea pig serum to anti-MC serum removed the precipitins against guinea pig serum and also against the homogenized lymph node filtrate. The anti-MC serum lost forthwith its ability to induce the Arthus phenomenon in guinea pig skin; however, it still induced erythema, edema, and cellular infiltration. Within twelve to twenty-four hours this reaction disappeared, leaving no trace of necrosis characteristic of the Arthus phenomenon.

Blood Counts.—Blood was obtained from a small incision on the guinea pig's ear. Hayem's solution was used as the diluent for red cell counts, and 3 per cent acetic acid was used for white cell counts. The counts were made in a Neubauer-Levy counting chamber. Wright's stain was used to stain smears, and at least 100 leukocytes were differentiated into polymorphonuclears, mononuclears, eosinophils, and basophils.

Experimental Animals.—The techniques used to sensitize guinea pigs with 2,4-dinitrochlorobenzene (DNCB) and to measure the contact sensitivity are described in detail in a previous study[2] from this laboratory. In twelve guinea pigs, one drop (0.025 ml.) of 0.5, 0.1, and 0.01 per cent DNCB in olive oil and plain olive oil was applied to shorn skin on one side of the back, the highest

*Freund's adjuvant complete (Difco Laboratories, Detroit, Michigan) containing 5 mg. of *Mycobacterium butyricum* in Mannide monoleate (1.5 ml.) and paraffin oil (8.5).

concentration in the rear. The results were read twenty-four hours after application of the test solutions. A test was considered positive if an erythema appeared. The reactions were gauged by induration of the dermis as follows: +++ = marked; ++ = distinct; and + = slight thickening.

Seven days after the epicutaneous testing, five guinea pigs were injected intracardially with 1 mm. of anti-MC serum, and seven guinea pigs were injected with normal serum. The injections were repeated twenty-four and sixty hours later, using 0.5 ml. of each serum. Blood counts were made prior to and three, six, twenty-four, thirty-six, fifty-four, sixty, and sixty-six hours after the first injection. Thirty-six hours after the first injections, the epicutaneous tests with DNCB solutions were repeated in a new freshly shorn area of the back. The results were read twenty-four hours later. (The criteria for gauging the tests were described above.)

RESULTS

The properties of the anti-MC serum are presented in Table I. Processing destroyed hemolysins and hemagglutinins against guinea pig erythrocytes and precipitins against guinea pig serum and lymph node filtrate. The anti-MC serum produced a skin reaction of the immediate type, but it had lost the ability to induce the Arthus phenomenon.

TABLE II. CHANGES IN THE NUMBER OF CIRCULATING LEUKOCYTES AFTER INJECTIONS OF ANTI-MONONUCLEAR CELL SERUM

GUINEA PIG NO.	HOURS AFTER FIRST INJECTION OF ANTISERUM											
	CONTROL	0	3	6	24	24	36	36	54	60	60	66
51	21,600	1 ml. AS injected	12,150	14,200	23,050	0.5 ml. AS injected	14,350	Patch test applied	11,400	12,000	Patch test read 0.5 ml. AS injected	10,400
52	19,550		11,800	16,550	11,650		16,500		10,700	9,350		12,300
54	11,000		4,500	5,900	16,200		10,550		11,650	13,200		7,100
55	27,950		13,600	19,700	20,650		16,800		9,450	9,450		7,900
56	14,050		17,950	18,550	14,350		19,400		16,950	9,475		9,800
Average	18,830		12,000	14,980	17,180		15,520		12,030	10,695		9,500

TABLE III. CHANGES IN THE NUMBER OF CIRCULATING MONONUCLEAR CELLS AFTER INJECTIONS OF ANTI-MONONUCLEAR CELL SERUM

GUINEA PIG NO.	HOURS AFTER FIRST INJECTION OF ANTISERUM											
	CONTROL	0	3	6	24	24	36	36	54	60	60	66
51	13,755	1 ml. AS injected	2,795	2,414	5,532	0.5 ml. AS injected	2,296	Patch test applied	5,016	6,240	Patch test read 0.5 ml. AS injected	1,976
52	12,267		1,888	1,655	3,146		2,805		2,782	4,021		2,460
54	8,084		1,305	1,121	5,994		1,899		4,777	6,996		994
55	22,111		4,760	3,546	8,054		1,680		6,143	4,820		2,528
56	7,488		3,590	2,412	4,879		1,746		5,085	5,211		2,058
Average	12,740		2,870	2,230	5,520		2,085		4,760	5,460		2,005

The blood changes after injection of anti-MC serum are tabulated in Table II (leukocytes), Table III (mononuclears), and Table IV (polymorphonuclears); the blood changes after injection of normal serum are shown in Tables V, VI, and VII. The averages of the blood cell counts at each interval are shown graphically in Fig. 1. Herein are contrasted the effects of injection of anti-MC serum and of normal serum on the number of leukocytes, mononuclears, polymorphonuclears, and eosinophils.

TABLE IV. CHANGES IN THE NUMBER OF CIRCULATING POLYMORPHONUCLEAR CELLS AFTER INJECTIONS OF ANTI-MONONUCLEAR CELL SERUM

GUINEA PIG NO.	HOURS AFTER FIRST INJECTION OF ANTISERUM											
	CONTROL	0	3	6	24	24	36	36	54	60	60	66
51	7,577	1 ml. AS injected	8,262	11,644	17,518	0.5 ml. AS injected	12,054	Patch test applied	6,384	5,760	Patch test read 0.5 ml. AS injected	8,320
52	7,067		9,086	13,902	8,272		13,530		7,811	5,236		9,840
54	2,181		3,195	4,602	10,206		8,546		6,641	5,940		6,106
55	5,071		7,208	15,563	12,390		14,784		3,308	4,442		5,293
56	4,627		12,385	14,284	9,471		17,460		11,696	3,980		7,546
Average	5,305		8,025	12,000	11,570		13,275		7,170	5,070		7,420

TABLE V. CHANGES IN THE NUMBER OF CIRCULATING LEUKOCYTES AFTER INJECTIONS OF NORMAL SERUM

GUINEA PIG NO.	HOURS AFTER FIRST INJECTION OF NORMAL SERUM											
	CONTROL	0	3	6	24	24	36	36	54	60	60	60
41	15,750	1 ml. NS injected	17,650	21,100	31,300	0.5 ml. NS injected	24,150	Patch test applied	19,050	21,000	Patch test read 0.5 ml. NS injected	20,000
42	11,550		22,650	18,650	11,450		7,250		8,400	15,350		17,450
43	16,800		14,900	24,250	23,800		14,550		15,650	14,700		11,600
44	17,850		27,650	14,300	16,450		8,900		14,500	17,100		19,650
45	15,500		16,800	27,850	19,600		10,350		14,550	12,650		13,450
46	15,500		30,325	21,950	11,800		10,450		7,400	7,500		8,700
47	12,750		18,700	19,100	13,400		16,600		9,900	9,350		13,650
Average	15,100		21,240	21,030	18,255		13,180		12,780	13,950		14,930

TABLE VI. CHANGES IN THE NUMBER OF CIRCULATING MONONUCLEAR CELLS AFTER INJECTIONS OF NORMAL SERUM

GUINEA PIG NO.	HOURS AFTER FIRST INJECTION OF NORMAL SERUM											
	CONTROL	0	3	6	24	24	36	36	54	60	60	66
41	7,490	1 ml. NS injected	5,525	3,587	16,902	0.5 ml. NS injected	13,524	Patch test applied	12,001	13,440	Patch test read 0.5 ml. NS injected	6,000
42	6,195		3,398	4,203	5,496		5,075		5,292	9,056		12,564
43	10,283		3,725	2,668	9,996		8,003		12,833	12,642		4,988
44	9,504		14,378	7,007	12,522		5,785		11,745	9,918		8,057
45	8,835		3,024	3,620	12,152		6,417		13,095	8,981		3,228
46	7,968		6,975	7,902	6,962		7,524		5,254	4,725		2,958
47	9,118		3,740	5,730	8,844		5,976		5,049	6,545		5,733
Average	8,485		5,825	4,960	10,410		7,470		9,325	9,330		6,220

TABLE VII. CHANGES IN THE NUMBER OF CIRCULATING POLYMORPHONUCLEAR CELLS AFTER INJECTIONS OF NORMAL SERUM

GUINEA PIG NO.	HOURS AFTER FIRST INJECTION OF NORMAL SERUM											
	CONTROL	0	3	6	24	24	36	36	54	60	60	66
41	7,185	1 ml. NS injected	11,305	17,302	13,772	0.5 ml. NS injected	9,901	Patch test applied	5,524	6,300	Patch test read 0.5 ml. NS injected	13,000
42	3,255		19,252	14,360	5,725		2,175		3,024	6,293		4,886
43	5,443		11,026	21,582	13,804		6,402		2,660	1,911		6,612
44	6,125		12,378	7,150	3,619		2,937		2,465	5,643		10,021
45	4,799		13,776	24,229	7,448		3,933		1,455	3,542		10,088
46	5,147		23,350	14,048	4,248		2,926		1,998	2,550		5,742
47	3,574		14,960	13,179	4,556		12,284		4,851	2,805		7,508
Average	5,075		15,150	15,980	7,595		5,795		3,140	4,150		8,265

The first intracardial injection of the anti-MC serum causes an 80 per cent depletion of mononuclear cells and a rise in polymorphonuclear cells and eosinophils. The disappearance of the mononuclears is greater than the increase of polymorphonuclears and eosinophils, resulting in moderate leukopenia. Against these changes stands the effect of intracardial administration of normal serum. Although there is a brief decrease (about 30 per cent) in mononuclear cells, the immediate and marked rise in polymorphonuclear cells results in leukocytosis. The immediate decrease in eosinophils after injection of normal serum is in contrast to the initial eosinophilia in animals injected with the anti-MC serum. The 80 per cent depletion of mononuclear cells in animals injected with the anti-MC serum has a lasting effect. Contrawise, the disappearance of mononuclears in animals injected with normal serum lasts only twenty-four hours; the number of mononuclears then returns to normal and does not change even with further serum injections.

In animals injected with the anti-MC serum, counts were continued for ten days after the first injection. The normal mononuclear cell count did not return during this period. A depletion of the basophils was observed after injection of both anti-MC serum and normal serum. The difference in the two groups was insignificant. In animals injected with anti-MC serum erythrocytes were counted prior to and three and sixty hours after the first injection. The red cell count remained unaffected and within the range of 5,100,000 to 5,800,000 cells per centimeter.

The animals of both groups were tested by epicutaneous application of DNCB in olive oil thirty-six hours after the first serum injection (Fig. 1). The test was read twenty-four hours later. In Table VIII are contrasted the results of epicutaneous testing with DNCB before and after injections of anti-MC serum; in Table IX the results of epicutaneous testing before and after injections of normal serum are shown.

It is apparent that the contact reactivity of animals treated with anti-MC serum is reduced, inasmuch as 0.5 per cent DNCB in olive oil has induced reactions comparable to those induced by 0.1 and 0.01 per cent DNCB in olive

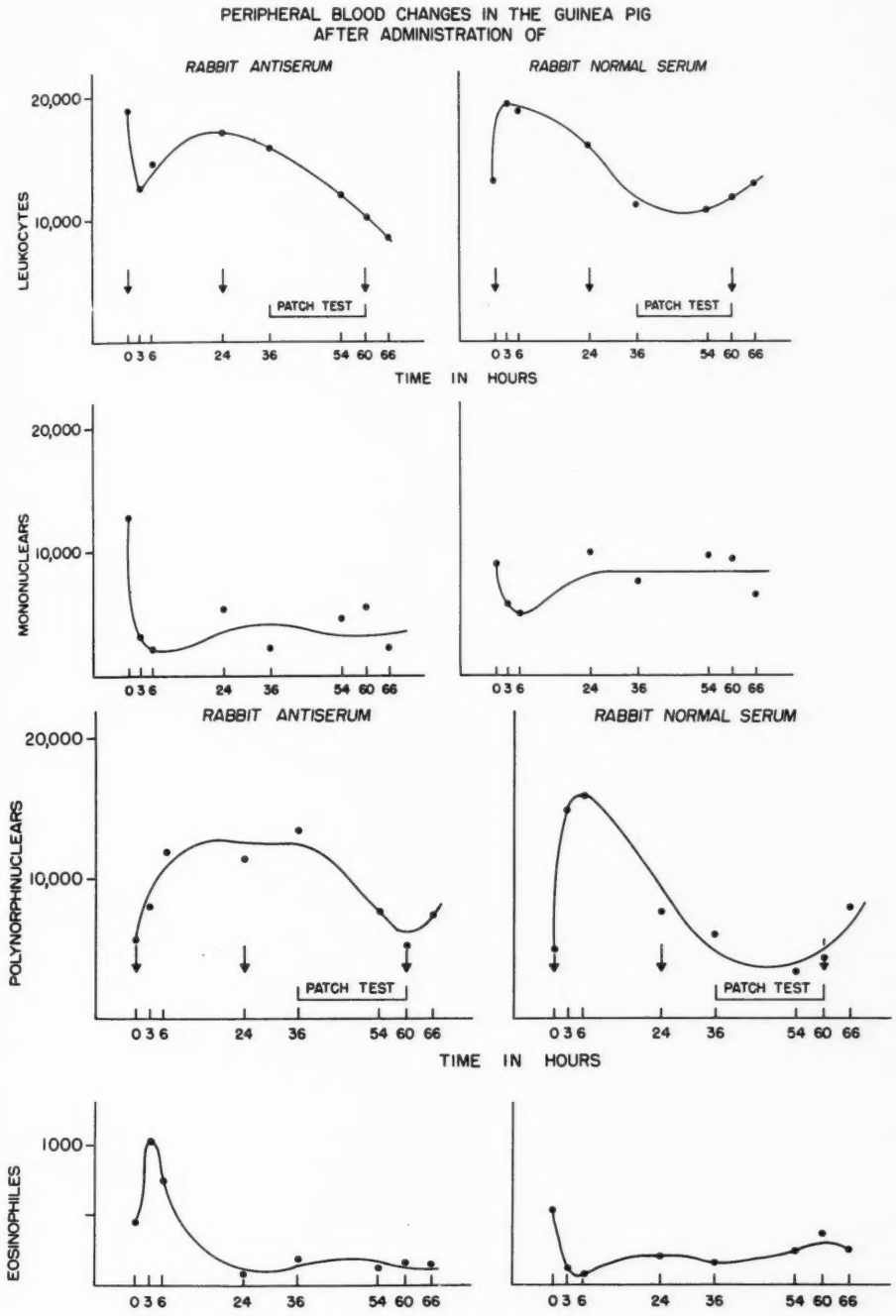
PERIPHERAL BLOOD CHANGES IN THE GUINEA PIG
AFTER ADMINISTRATION OF
RABBIT ANTISERUM
RABBIT NORMAL SERUM
LEUKOCYTES
20,000
10,000
PATCH TEST
0 3 6
24
36
54 60 66
TIME IN HOURS
MONONUCLEARS
POLYNORPHNUCLEARS
EOSINOPHILES
1000

Fig. 1.

TABLE VIII. THE RESULTS OF EPICUTANEOUS TESTS WITH THREE DIFFERENT DNCB CONCENTRATIONS OF SENSITIZED ANIMALS BEFORE AND AFTER INJECTIONS OF ANTI-MONONUCLEAR CELL SERUM

GUINEA PIG NUMBER	CONCENTRATION OF DNCB IN OLIVE OIL (PER CENT)					
	BEFORE INJECTION			AFTER INJECTION		
	0.5	0.1	0.01	0.5	0.1	0.01
51	+++	++	+	++	+	–
52	+++	++	+	+	–	–
54	++	++	–	+	–	–
55	++	++	+	+	–	–
56	++	+	+	+	–	–

oil seven days prior to the injections. The 80 per cent depletion of mononuclear cells is accompanied by a ten- to fifty-fold reduction in allergic contact sensitivity as gauged by the antigen concentrations needed to induce a comparable positive reaction. No significant change in the contact reactivity has occurred in the animals injected with normal serum.

TABLE IX. THE RESULTS OF EPICUTANEOUS TESTS WITH THREE DIFFERENT DNCB CONCENTRATIONS ON SENSITIZED ANIMALS BEFORE AND AFTER INJECTIONS OF NORMAL SERUM

GUINEA PIG NUMBER	CONCENTRATION OF DNCB IN OLIVE OIL (PER CENT)					
	BEFORE INJECTION			AFTER INJECTION		
	0.5	0.1	0.01	0.5	0.1	0.01
41	++	+	+	++	++	+
42	+++	++	+	++	+	+
43	+++	++	–	+++	++	–
44	+++	+	–	++	+	+
45	++	+	–	++	+	–
46	++	+	–	++	+	–
47	+	–	–	++	+	–

DISCUSSION

The observed depletion of mononuclear leukocytes induced by injection of rabbit anti-guinea pig mononuclear cell serum coincides with a significant reduction in allergic contact reactivity. Thus, the degree of allergic contact reaction is conditioned by the number of circulating mononuclear cells, as Inderbitzin[7] has demonstrated by the tuberculin reaction.

Histopathologic and chemical studies show that changes characteristic of allergic contact dermatitis take place in the absence of polymorphonuclear cells.[2-4, 7] A clear-cut confirmation that allergic contact dermatitis runs its course independently of polymorphonuclears was not borne out in the reported experiments. At the time of epicutaneous testing of animals depleted of mononuclear cells, a twofold increase in polymorphonuclears was observed. The mononuclear cells did not disappear completely; nor did the allergic contact sensitivity. It is impossible to determine whether the remaining sensitivity was due solely to the remaining mononuclear cells or whether it was influenced in some way by the increase in polymorphonuclear cells. Of special interest in this connection is the study by Pepy,[8] who showed that depletion of polymorphonuclears does not influence the onset and the development of

tuberculin skin reaction, whereas Favour[9] recently demonstrated in vitro a lysis of polymorphonuclear cells of tuberculin-sensitive animals upon challenge with a nontoxic concentration of PPD.

At the site of epicutaneous testing a depletion of eosinophils was observed in all animals injected with either serum. Since the cutaneous reactivity of animals depleted of mononuclears is decreased, whereas that of the control group is unchanged, it seems that the number of eosinophils has no influence on the allergic contact reactivity. The same holds true for the basophils.

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BUCCAL MUCOSAL TESTS IN PATIENTS WITH CANKER SORES (APHTHOUS STOMATITIS)

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RECURRENT canker sores (aphthous stomatitis) are common in children and young adults, but their specific etiology is not known. Mention is made in textbooks[1, 2] of the repeated failure to demonstrate a virus etiology; furthermore, the available though scant histopathologic studies suggest an eczematous rather than a viral etiology. Allergic etiology has been considered but has not been proved. There is general agreement, however, that excessive ingestion of such foods as citrus fruits, melons, tomatoes, vinegar, wine, chocolate, and nuts (walnuts) seems to play a role in the formation of the ulcers. The avoidance of these foods is generally recommended in treatment. The pathologic nature of the mouth lesion would lead one to surmise that if the cause is allergic, ulcer formation takes place by means of direct contact, for the lesion resembles a vesicle rather than an urticarial wheal.

Other suggested etiologies include (1) avitaminosis, since improvement at times follows vitamin B or C therapy, and (2) bacterial infections, since diplococci and streptococci are found in cultures from the lesions.

The canker-sore lesions begin as small, single or multiple, yellow-gray papulovesicles 2 to 3 mm. in size. These lesions are quite sensitive. Within a few hours they change into tender ulcerations, which is the way they usually appear by the time they are inspected. The sites most often involved include the buccal mucosa, the edges of the tongue, the gingivae, and the palate. The oral lesions appear in successive crops at irregular intervals, sometimes over a period of years. They heal without scarring in a week or two. Occasionally, they may be so painful as to interfere with speech or with mastication. Some patients have concomitant gastrointestinal symptoms, including epigastric discomfort, pain, nausea, and flatulence; occasionally there is associated erythema nodosum.

In 1956 Tuft and Ettleson[3] reported the results of a clinical study of an allergic patient who had recurrent canker sores of the mouth for many years. They were able to reproduce these ulcers by direct application of citric acid and acetic acid to the buccal mucosa, and thus they proved the etiological relationship of these agents to the canker sores. Their results with that patient prompted further investigations into the possibility of utilizing this method of testing as an aid in etiological diagnosis not only in patients with canker sores but perhaps also in patients with other forms of allergy to food or drugs. We wish, in the present communication, to report the results of our studies in patients with recurrent canker sores.

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METHOD OF STUDY

Technique.—Since this was a pilot study, various methods were tried, and the following technique was evolved: We placed 0.5 cm. of testing material, if crystalline (as in the case of citric acid and tartaric acid), or a 0.5 cm. cotton pledget saturated with the liquid organic acid (as in the case of acetic acid, vinegar, or lactic acid) on the anterior buccal mucosa on either side of the frenulum of the lip and as far laterally (1 cm.) from the frenulum of the lower lip as possible in order that two tests could be done at one time (Fig. 1). The space utilized is formed by the junction of the lower lip and the lower anterior alveolar surface. The cotton pledgets were introduced with a blunt forceps, and the crystals were introduced with a tongue depressor divided lengthwise so that it was about 1 cm. wide. The test material was removed at the end of three minutes which, after numerous trials, was found to be the most satisfactory interval. We tested only four organic acids—citric, acetic, tartaric, and lactic—since these are commonly found in foods. Citric and tartaric acids were tested in powder form. Acetic acid was tested as a 5 per cent solution or as vinegar. Lactic acid was tested as 0.1 normal solution (pH 2.4), which approximates the concentrations usually used in food recipes.

Fig. 1.—Technique of application of test material.

The patients chosen included (1) randomly selected nonallergic patients admitted to the medical wards for diagnostic study and used in our series as controls and (2) unselected allergic patients in the outpatient allergy clinic

and hospital wards. All patients were tested, whenever possible, with all four organic acids. Patients in both the control and the allergic groups were questioned closely, to find out not only whether they had any personal allergic manifestations but especially whether they were subject to canker sores. Only one patient (Case 2, Patient M. R.) was seen primarily because of the canker sores.

REACTIONS

Positive.—If a canker-sore lesion was produced at the site of the organic acid, the reaction was considered definitely positive (Fig. 2). In such instances an area of redness and desquamation was first noted within three to twenty minutes. This became ulcerative in twenty-four to forty-eight hours. It usually lasted about one week.

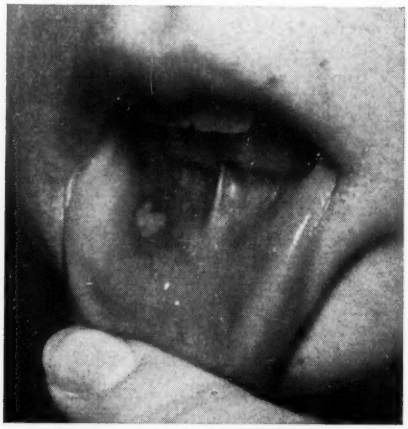

Fig. 2.—Positive reaction with reproduction of canker sore after application of citric acid in Case 3.

Negative.—When no symptoms were noted in three to twenty minutes and again after twenty-four and forty-eight hours, the reaction was considered negative.

Doubtful.—Many patients manifested the following changes: variable degrees of erythema, edema, and tenderness as mapped out with a tongue depressor, going on to exfoliation in some but never developing into a canker sore.

The reactions in such patients usually appeared within three to twenty minutes and disappeared within twenty-four or forty-eight hours after the application of the test substance. Occasionally the change was observed after twenty-four or forty-eight hours as a delayed reaction and lasted a short time, but this was the exception rather than the rule. Although we recorded these reactions as doubtful, they were included in our statistical evaluation as negative.

RESULTS

A summary of our findings is shown in Tables I and II. Inspection of the latter reveals at once that a definite positive reaction with the induction of a canker sore appeared in those patients tested with citric and acetic acids but not with tartaric or lactic acids. This was true not only for the patients in the allergic group and in the nonallergic control group but also for those patients with a positive history of canker sores; therefore, one can assume that lactic and tartaric acids probably have little or nothing to do with the causation of canker sores.

TABLE I. RESULTS OF MUCOSAL TESTS WITH ORGANIC ACIDS

TEST MATERIAL	TYPE OF PATIENT	NUMBER TESTED	POSITIVE HISTORY OF CANKER SORES	POSITIVE REACTIONS (CANKER SORES)
Citric acid	Allergic	108	46	8
	Nonallergic	57	4	0
Acetic acid	Allergic	96	35	6
	Nonallergic	37	2	0
Tartaric acid	Allergic	94	43	0
	Nonallergic	39	0	0
Lactic acid	Allergic	52	18	0
	Nonallergic	32	0	0

Especially noteworthy is the high incidence (almost 50 per cent) of a positive history of canker sores in the allergic group as contrasted with the nonallergic control group (less than 10 per cent). This would suggest that in many patients canker sores are allergic in origin.

TABLE II. TEST RESULTS IN PATIENTS WITH CANKER SORES

TEST MATERIAL	TOTAL TESTS	ALLERGICS	POSITIVE TEST (CANKER SORE)
Citric acid	49	46	6
Acetic acid	37	35	4
Tartaric acid	43	43	0
Lactic acid	18	18	0

Another interesting observation shown in the tables is that the positive tests with both citric and acetic acids occurred only in allergic patients and not in the nonallergic control patients. Analysis of the positive tests shown in Table III shows that seven patients had a positive history of canker sores and that three did not. In the former group, three had positive test reactions to both acids, two were positive to citric acid and negative to acetic acid, and one was positive to acetic acid and not to citric acid. One patient refused to be tested to acetic acid after having a positive reaction to the citric acid. Of the three patients with negative histories of canker sores, one gave a positive test reaction to both acids and the other two refused further testing after having had a positive test reaction. These results suggest that patients with

canker sores may, and perhaps often do, have positive test reactions to both citric and acetic acids but that they may have a positive reaction to only one acid.

TABLE III. ANALYSIS OF POSITIVE TESTS IN CANKER-SORE PATIENTS (ALL ALLERGIC)

PATIENT	CANKER SORE HISTORY	CITRIC ACID	ACETIC ACID
E. S.	All negative	+	Not tested
G. R.		+	+
B. B.		Not tested	+
G. S.	All positive	+	Negative
C. K.		+	+
J. R.		+	+
M. R.*		+	+
E. S.		+	Not tested
G. D.		+	Negative
I. O.		Negative	+

*Patient's primary complaint was canker sores.

The signs of irritation which were seen within a short time after the application of the test materials and which we termed doubtful reactions were observed in a substantial group of patients, both allergic and nonallergic, regardless of the test material used. However, such reactions appeared more often in the allergic group (58.3 per cent for citric acid and 47.9 per cent for acetic acid) than in the nonallergic or control group (14 per cent for citric acid and 13.5 per cent for acetic acid). This difference between the two groups was wide enough to be statistically significant.

COMMENT

The results of the present investigations confirm the findings presented in the original case report by Tuft and Ettleson[3] and add some new features. Thus, in a group of allergic patients we were able to produce canker sores repeatedly in six patients by direct mucosal contact tests with citric acid and in four patients by tests with acetic acid. All these patients had positive histories of recurrent canker sores similar to those reproduced by the tests. Three patients had a positive test reaction with a negative history for canker sores. The reason for this is unexplained. By contrast, tests with the citric and acetic acids in nonallergic control patients failed to produce canker sores; likewise, tests with tartaric and lactic acids did not produce canker sores in any patients, indicating that they apparently were not of etiological importance in relationship to the canker sores. This was further verified clinically by the improvement which followed the elimination from the diet of foods containing citric and/or acetic acids, as in the illustrative case reports that follow.

CASE REPORTS

Case 1.—Patient J. C.,* aged 37 years,was first seen in May, 1954, with allergic rhinitis, asthma, migraine, and a history of canker sores in the mouth since early childhood. Repeated

*This patient was the subject of the original study reported in 1956 by Tuft and Ettleson.[3] This case is included here because of further follow-up observations.

tests with both citric and acetic acids were strongly positive, with the reproduction of a canker sore in each instance that persisted for seven to ten days. Subsequent clinical trials with various foods determined that canker sores could be provoked not only by commercial foods or recipes containing citric or acetic acids but also after the ingestion of oranges, grapes, dried apricots, raw and canned peaches, pineapple, wines (especially Chianti), brandies, beer, and most mixed alcoholic drinks, as well as foods containing vinegar, such as cole slaw, potato salad, or beef cooked in vinegar. By contrast also, the patient found that he could eat beef with impunity, as well as raw or cooked apples, raw or canned pears, cantaloupe, watermelon, honeydew melon, Persian melon, and raw celery. The latter finding is of interest, since these are in the class of "acid" foods often considered causes of canker sores.

Following the diagnostic study, and especially after the determination by extensive clinical trials of the offending factors, the patient eliminated from his diet, as far as possible, all known offending factors as well as those which, so far as could be determined from the labels on packaged or canned foods, containing no citric or acetic acid. During the nearly four-year period that has elapsed he has had far fewer canker sores, and most of those could be traced to dietary indiscretion, either intentional or accidental.

Case 2.—Patient M. R., aged 27 years was first seen on Feb. 5, 1953, with allergic rhinitis and spring and fall hay fever. She has had recurrent crops of canker sores (eight to ten at a time) for fourteen years and seldom was free of them. The patient noticed that ulcers were worsened by ingestion of tomatoes, pineapple, chocolate, nuts, and raw fruits (for example, peaches, apples, etc.) but not apparently by cooked or canned fruit. Following the trial elimination of milk, cheese, nuts, spices, raw fruits, and uncooked vegetables from the diet, there was marked improvement with considerably fewer ulcers, and for the first time in years the patient would be completely free of canker sores for periods of up to two weeks. Of particular interest was the fact that a "common cold" associated with fever was followed by the appearance of a crop of ulcers which the patient attributed to the "cold." However, inquiry revealed that, because of the "cold," she took large amounts of fresh juices for several days and the ulcers did not appear until that time.

In February, 1956, when the mouth was free of ulcers, the patient tried testing herself, after proper instructions (since she lived at a distance and could not come in for the tests), with a crystal of citric acid. Instead of leaving it in her mouth for three minutes, however, she left it in for thirteen minutes. This was followed within twenty-four hours by a large ulcer which took some time to heal. When this cleared up, she tested herself with vinegar. This likewise produced a canker sore. The patient at this time noted that foods containing vinegar (for example, cole slaw) induced crops of ulcers. Following these determinations, the patient eliminated from her diet all foods containing citric or acetic acids as well as those which she found, by clinical trial, also caused ulcers (such as watermelon, cantaloupe, corn on the cob, nuts, etc.). In November, 1957, she reported that for a period of almost six months she was practically free of ulcers, with only a very mild occasional one after dietary indiscretion (candy apples, for example).

Case 3.—Patient E. S., aged 20 years, was seen in October, 1957, because of ragweed hay fever and asthma. For several years she has been subject to single or multiple canker sores, occurring at any time but coming more frequently in the summer. The patient herself attributed the summer outbreaks to excessive ingestion of fresh fruits and fruit juices, notably orange juice. The buccal mucosal test with citric acid was positive with reproduction of the canker sore (Fig. 2). No test was done with acetic acid. Following the elimination of foods containing citric acid, the patient remained free of canker sores.

All of these case reports are noteworthy because of the marked improvement which followed the complete elimination from the diet of foods containing citric acid and/or acetic acid. This was especially striking in Case 2. Although there was considerable reduction in the number and severity of the

canker sores following elimination of foods suspected of causing the ulcers, complete disappearance of the ulcers did not occur until she eliminated all foods containing citric and acetic acids after having a positive mucosal test. Of special interest in this patient was her experience after having a "common cold." Since this was followed by a crop of canker sores, the natural tendency is to link the latter with the "cold" and attribute it to a viral etiology. In this instance, however, the patient ingested a large amount of citric-acid-containing juices, as is commonly prescribed in the treatment of the "common cold," and the canker sores did not appear until afterward. In this case, therefore, it would seem more likely that the canker sores were provoked by the fruit juices rather than by a virus, and this might explain the reason for the canker sores in other patients with "colds" in whom a viral etiology formerly was suspected.

1. Fruits: citrus fruit
2. Artificial-fruit-flavored drinks (Kool-Aid), hard candy
3. Preservatives
4. Carbonated water: ginger ale, club soda, Coca-Cola (Hires root beer is an exception)
5. Candy: commercial chocolate (Baker's chocolate used in pastry and candy is an exception), red-colored Smith Brother's cough drops, lollipops, Life Savers, hard candy
6. Medication: Alka-Seltzer and Bromo-Seltzer

Fig. 3.—Foods containing citric acid.

Since both citric and acetic acids are used widely in cooking and in the diet, it is important that the patient be acquainted with the foods containing these agents. Foods containing citric acid are listed in Fig. 3, and those containing acetic acid are listed in Fig. 4. (Figs. 3 and 4 were prepared with the aid of our dietary department.) These lists are not complete; no doubt many other commercial foods contain citric and acetic acids. However, canker-sore patients found sensitive to these substances should be warned to read the labels on all canned or bottled foods before eating those foods to see if these substances are present.

1. *Dressings* such as those used in potato salad and cole slaw, catsup (also contains citric acid)
2. *Sauces:* Tartar sauce, hollandaise, chili sauce, and Worcestershire sauce, mustard.
3. *Pickled foods:* (a) corned beef, (b) relish, pickled cucumbers, Harvard beets, pigs feet, baked beans, sauerbraten.

Fig. 4.—Foods containing acetic acid.

Another interesting feature of our study was the high incidence of canker sores in the group of allergic patients as contrasted with the lower percentage in nonallergic control patients. This would suggest a possible allergic basis for the lesions in some patients.

As already indicated, what we designated as a doubtful reaction was hard to evaluate. In such patients the application of the test material, especially

citric acid, seemed to induce a subsequent inflammatory reaction of variable intensity and duration which subsequently disappeared without developing into a definite canker sore. We termed this reaction doubtful, since it was distinctly different from a clear-cut negative reaction and yet did not reproduce the positive canker sore. It appeared too frequently in the patients tested to be considered etiologically specific, and it may have been due to the irritating nature of the test materials. However, the significantly higher incidence of this reaction in the allergic group of patients suggests a possible difference in the tissue response of the latter as compared to that of the nonallergic control patients. Whether this merely indicated that the allergic mucous membrane is more irritable and more easily sensitized is difficult to say and awaits further study.

As indicated in our previous report, one might question the modus operandi by which these organic acids produce the canker sore. Since the ulcer was produced after direct contact of the acid with the mucosa, it must be assumed that this is a direct contact type of reaction, that is, a contact stomatitis similar perhaps to contact allergic dermatitis; in fact, the lesion produced is of the vesicular rather than the urticarial type. Once the patient becomes sensitized, however, recurrence might take place not only from direct contact but even after the agent is ingested, just as is true, for example, of contact dermatitis due to mercury or arsenic.

The demonstration that the buccal mucosa can be utilized for the detection of allergy to organic acids makes it possible to employ this method in other forms of allergy in which skin tests are not helpful, as, for example, to detect sensitization to other food ingredients in patients with positive clinical histories and negative skin test reactions and also perhaps in patients with drug allergy in whom skin tests either cannot be done or are consistently negative. Investigation of the latter possibility is being carried out and will be the basis of a subsequent separate report.

SUMMARY

1. The buccal mucosal contact test with organic acids (citric and acetic) was found diagnostically useful in patients subject to recurrent canker sores (aphthous stomatitis). The latter were reproducible in six of the forty-six canker-sore patients tested with citric acid and in four of the thirty-five patients tested with acetic acid.

2. Tartaric acid and lactic acid gave negative tests and were not considered of etiological importance.

3. A history of canker sores was much more frequent in allergic patients than in nonallergic control patients. None of the nonallergic patients in the control group had a positive reaction, that is, a canker sore, as a result of the test.

4. The possible utilization of this method of testing in the diagnosis of food allergy in skin-test-negative patients and in drug allergy is indicated.

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CLINICAL EXPERIENCE WITH PARABROMDYLAMINE MALEATE (DIMETANE), A NEW ANTIHISTAMINIC

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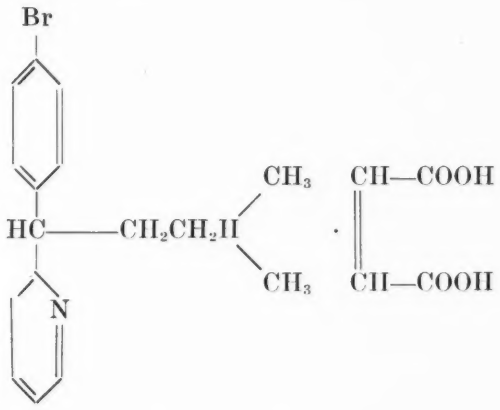
A NEW antihistaminic agent, parabromdylamine maleate (Dimetane),* has recently been introduced into clinical medicine. The purpose of this article is to report our experience with this new drug in a variety of allergic disorders.

This compound is known in the German literature as Ilvin, and its chemical name is 1-(p-bromophenyl)-1-(2-pyridyl)-3-dimethylaminopropane. The structural formula is shown below:



GENERAL PLAN OF STUDY

This report summarizes the results obtained with Dimetane in various allergic disorders in patients studied by us at the Beekman-Downtown Hospital and in private practice. A total of eighty-two patients were observed. Their ages ranged from 6½ to 73 years, and the group consisted of thirty-nine male and forty-three female patients.

In all cases the symptoms have been shown by history and/or skin testing to be on an allergic basis. In most instances the patients have been followed by one or more of the observers for periods ranging from several months to several years, and many have previously been studied for the effects achieved by established and experimental therapeutic agents.

From the Allergy and Chest Clinics of the Beekman-Downtown Hospital, New York, New York.

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*The Dimetane employed in this study was supplied through the courtesy of Drs. James O. Burke and Jack Freund, Medical Department, A. H. Robins Co., Inc., Richmond, Virginia.

TABLE I. SUMMARY OF USE OF BROMDYLAMINE

NO.	PATIENT	AGE	SEX	DIAGNOSIS	PREPARATION	DURATION OF ADMINISTRATION	RESPONSE	COMPARABLE EFFECTIVENESS OF REGULAR TABLETS AND EXTENTABS
1	S. A.	16	M	VMR and asthma	Reg.	1 month	Excellent—complete relief	
2	B. B.	18	F	VMR	Reg. and Ext.	4 months	Excellent to fair	No preference
3	A. B.	14	M	VMR	Reg. and Ext.	3 weeks	Moderate	Preferred regular tablets
4	J. B.	50	M	VMR and asthma	Reg. and Ext.	1 week	Moderate	No preference
5	B. D.	74	M	VMR and asthma	Reg. and Ext.	2½ months	Good to moderate	Preferred regular tablets
6	S. F.	65	F	VMR	Reg. and Ext.	2 months	Good to moderate	Preferred Extentabs ("more reliable")
7	R. F.	28	F	VMR	Reg. and Ext.	1 month	Good to moderate	Regular tablet more effective
8	H. F.	14	M	VMR	Ext.	2 weeks	Good to moderate	
9	M. F.	62	F	VMR	Reg. and Ext.	1 month	Good	No preference
10	C. G.	10½	M	VMR	Reg. and Ext.	3½ months	Good	Slight preference for regular tablets
11	L. G.	50	M	VMR	Reg.	3 weeks	Moderate to slight	
12	D. G.	9½	M	VMR	Reg. and Ext.	4 weeks intermittently	Slight to none	Questionable preference for Extentabs
13	M. J.	39	F	VMR, angioneurotic edema (?)	Reg. and Ext.	3 months	Moderate	No preference
14	I. K.	57	F	VMR and asthma	Reg.	1 week	None	
15	R. L.	14	M	VMR	Reg.	1 week	Good	
16	M. M.	57	F	VMR and asthma	Reg. and Ext.	2 weeks	Good	Slight preference for Extentabs
17	M. M.	13	M	VMR and asthma	Reg. and Ext.	2 weeks	Moderate	Preferred Extentabs
18	N. M.	73	M	VMR	Reg. and Ext.	5 months	Excellent	Preferred Extentabs
19	L. P.	13	M	VMR	Reg. and Ext.	5 months intermittently	Good	Preferred Extentabs
20	C. P.	28	F	VMR and asthma	Reg.	2 weeks	Good	
21	L. S.	10	F	VMR and asthma	Reg. and Ext.	6 months intermittently	Excellent	Preferred Extentabs

Key to Abbreviations:
VMR = Vasomotor rhinitis.
PBZ = Pyribenzamine.
CT = Chlor-Trimeton.

(DIMETANE) IN ALLERGIC DISORDERS

COMPARISON WITH OTHER ANTIHISTAMINIC DRUGS	DEVELOPMENT OF TOLERANCE	SIDE EFFECTS	COMMENTS
	None	None	
Equivalent to CT	2-3 weeks; similarly to various antihistaminics	None	Excellent response to all antihistaminics with fairly rapid development of tolerance
		None	
		None	Nasal stuffiness and discharge improved; itching of eyes not relieved
Superior to CT and PBZ	None	None	
Superior to CT	None	None	Good control on one Extentab b.i.d.
Superior to CT	None	Heartburn on 1 or 2 occasions only	Response somewhat irregular with effective duration from ½ to 4 hours, usually the longer period
Superior to CT	Moderate diminution of intensity and duration of effect toward end of test period	None	Similar development of tolerance to other antihistaminics
Superior to PBZ	None	None	Good relief on either form for 1½ hours; note larger total dose of Extentabs
Superior to PBZ	Slight loss of potency toward end of period	None	Regular form more effective but adequate relief by Extentab throughout school day
Slight preference over PBZ		None	
Poor response to all antihistaminics		None	Head pain (sinusitis?) and nasal stuffiness moderately relieved; no definite angioneurotic edema during test period (history only)
Equivalent to CT	None	None	
Prefers CT		None	Neither VMR nor asthma relieved
		None	
		None	Asthma inactive during period of observation
Slightly inferior to CT	None	Macular eruption of arms; disappeared 3 days after drug stopped	Similar eruptions previously noted; relation to drug therapy not definitely established
Superior to CT and Thephorin	None	None	Marked enthusiasm by patient—previously nonresponsive
Initially superior to CT; later, with tolerance, inferior	Slow development	None	Slow development of tolerance to all antihistaminics
Equivalent to PBZ	None	None	Did not produce drowsiness as did PBZ
Superior to CT	None	None	

TABLE I—

NO.	PATIENT	AGE	SEX	DIAGNOSIS	PREPARATION	DURATION OF ADMINISTRATION	RESPONSE	COMPARABLE EFFECTIVENESS OF REGULAR TABLETS AND EXTENTABS
22	G. S.	10	M	VMR	Reg. and Ext.	3 months	Moderate	Preferred Extentabs
23	A. S.	28	F	VMR	Reg. and Ext.	1 month	Excellent	Preferred Extentabs
24	V. S.	43	F	VMR and hay fever	Reg. and Ext.	2 weeks	Good	Preferred Extentabs
25	Y. S.	28	F	VMR	Reg. and Ext.	2 weeks	Slight	No preference
26	R. S.	20	F	VMR and hay fever	Reg. and Ext.	1 week	Good	One Extentab gave relief lasting all day
27	M. S.	64	F	VMR	Reg.	1 week	Slight to none	
28	H. S.	63	F	VMR	Reg. and Ext.	2 weeks	Good	Preferred regular tablets
29	C. V.	10	M	VMR	Reg. and Ext.	5 weeks	Excellent to good	Preferred regular tablets
30	R. V.	12	M	VMR	Reg.	2 weeks	Moderate	
31	H. W.	15½	M	VMR and inactive asthma	Reg.	2 weeks	Slight	
32	J. W.	63	F	VMR	Reg.	2 months	Good	
33	S. Z.	13	M	VMR	Reg.	1 month	Good	
34	T. B.	30	F	VMR	Reg.	2 months	Excellent	
35	N. C.	38	F	VMR and inactive asthma	Reg.	2 weeks	Good	
36	B. C.	13	M	VMR and asthma	Reg.	1 week	Excellent	
37	N. DeM.	29	F	VMR	Reg.	1 week	Poor	
38	M. F.	45	F	VMR	Ext. b.i.d.	1 week	Moderate	
39	W. I.	53	F	VMR	Ext. b.i.d.	1 week	Excellent	
40	S. P.	35	M	VMR	Reg. and Ext.	2 weeks	Good	
41	D. N.	30	F	VMR	Ext. at bedtime	2 weeks	Excellent	
42	L. N.	18	M	VMR	Reg. and Ext.	2 weeks	Excellent	Preferred Extentabs
43	G. M.	10	M	VMR	Reg. and Ext.	2 months intermittently	Slight	
44	P. Y.	10	M	VMR	Ext.	2 weeks	Excellent	
45	M. Z.	60	F	VMR and asthma	Ext.	2 weeks	Moderate for VMR; no effect on asthma	
46	R. R.	35	F	VMR	Reg.	2 weeks	Excellent	
47	M. W.	30	F	VMR	Reg.	2 weeks	Moderate	
48	M. S.	38	M	VMR	Reg.	1 week	None	
49	S. S.	45	M	VMR	Reg.	2 weeks	Slight	
50	A. P.	50	M	VMR	Reg.	2 weeks	Good	
51	B. P.	60	F	VMR	Reg.	2 weeks	Slight	
52	R. H.	38	F	VMR	Ext.	2 weeks	Moderate	
53	F. G.	58	F	VMR	Reg.	1 week	None	
54	A. S.	36	F	VMR and inactive asthma	Reg.	2 weeks	Good	
55	A. B.	54	F	Urticaria of undetermined origin, inactive asthma, VMR	Reg.	2 months	Moderate	

CONT'D

COMPARISON WITH OTHER ANTIHISTAMINIC DRUGS	DEVELOPMENT OF TOLERANCE	SIDE EFFECTS	COMMENTS
	None	None	
	None	None	
Preferred to PBZ	None	None	No drowsiness as with PBZ
Poor response to all antihistaminics	None	Slight drowsiness	
	None	None	
No response to several antihistaminics		None	
Preferred PBZ	None	Slight drowsiness on Extentabs	Moderate drowsiness on PBZ (25 mg. dosage)
	None	None	
	None	None	
Equivalent to CT		None	
Equivalent to PBZ	None	None	
	None	None	
	None	None	
	None	None	
	None	None	
	None	None	Brief and incomplete relief
	None	None	
	None	None	
Equivalent to PBZ	None	None	Moderate drowsiness on PBZ
	None	None	
Superior to PBZ	None	None	Mild drowsiness on PBZ
Slightly inferior to CT	None	None	
		None	
Superior to PBZ		None	
Superior to CT		None	
Equivalent to PBZ	None	None	
		Drowsy and listless	
Inferior to CT	None	None	
Superior to CT	None	None	
Inferior to CT		None	Poor response to all therapy
Equivalent to CT	None	None	
		None	
Superior to CT	None	Occasionally slightly drowsy	Asthma not a problem during period of study
Equivalent to PBZ	None	None	Slightly drowsy on PBZ

TABLE I—

NO.	PATIENT	AGE	SEX	DIAGNOSIS	PREPARATION	DURATION OF ADMINISTRATION	RESPONSE	COMPARABLE EFFECTIVENESS OF REGULAR TABLETS AND EXTENTABS
56	R. B.	36	M	VMR, recurrent urticaria	Reg.	3 weeks	Good for both conditions	
57	L. B.	44	M	VMR	Ext.	5 weeks	Excellent; 1 tablet gave relief for entire day	
58	M. H.	22	F	Hay fever	Reg. and Ext.	1 week	Slight	Preferred Extentabs although relief slight
59	L. M.	18	F	Hay fever and VMR	Reg. and Ext.	2 months	Excellent	Slight preference for regular tablets
60	L. A.	9	M	Hay fever	Reg.	2 weeks	Good	
61	E. B.	20	F	Hay fever	Reg., 4 mg. b.i.d.	2 weeks	Excellent	
62	M. B.	45	M	Hay fever	Reg. and Ext.	3 weeks	Excellent	No preference
63	A. B.	34	F	Hay fever	Reg. and Ext.	2 weeks	Good to moderate	Preferred Extentabs
64	M. F.	24	F	Hay fever and rose fever	Ext.	3 weeks	Excellent	
65	V. O.	30	M	Hay fever	Ext.	2 weeks	Excellent	
66	J. L.	13	M	Hay fever	Reg. and Ext.	3 weeks	Good	Marked preference for Extentabs
67	D. V.	15	M	Hay fever	Reg.	2 weeks	Marked (excellent)	
68	M. P.	28	F	Hay fever	Reg.	2 weeks	Slight	
69	M. N.	26	F	Hay fever	Reg.	2 weeks	Moderate	
70	J. M.	40	M	Hay fever	Reg.	2 weeks	Slight	
71	M. K.	28	M	Hay fever	Reg.	3 weeks	Slight	
72	E. F.	32	M	Hay fever	Reg.	2 weeks	Moderate	
73	A. B.	18	F	Hay fever	Reg.	1 week	None	
74	M. B.	24	F	Hay fever	Reg.	1 week	None	
75	E. M.	32	M	Hay fever	Reg.	2 weeks	Good	
76	R. I.	40	F	Pollen asthma	Ext. b.i.d.	4 weeks	Moderate to slight	
77	E. V.	6	M	Allergic cough	Reg.	2 weeks	Good	
78	W. S.	42	M	Asthma	Reg.	1 week	None	
79	R. T.	58	F	Allergic cephalalgia	Ext.	2 weeks	Indeterminate	
80	B. C.	32	F	Angioneurotic edema	Reg. and Ext.	2 weeks	Moderate	No preference
81	C. W.	60	M	Urticaria, penicillin (?)	Reg.	1 week	Good	
82	J. S.	6½	F	Chronic urticaria	Reg.	1 week	Good	

CONT'D

COMPARISON WITH OTHER ANTIHISTAMINIC DRUGS	DEVELOPMENT OF TOLERANCE	SIDE EFFECTS	COMMENTS
Superior to PBZ with less side effects	None	Occasional slight drowsiness	More comfortable on Dimetane, much less drowsiness
Superior to PBZ and CT	None	None	Complete relief of nasal stuffiness for first time in many months
		None	
Superior to CT	None	None	
	None	None	
	None	None	
Preferred to CT	None	None	
	None	None	
	None	None	One Extentab often adequate for entire day
Superior to PBZ	None	None	Complete relief afforded day and night
Superior to PBZ	None	None	
		None	
Superior to CT, PBZ, and others	None	None	
Equivalent to CT and PBZ	None	None	
Slightly superior to CT		None	Poor response to all antihistaminics
No relief on PBZ		None	Symptoms very severe during pollen period
Equivalent to CT		None	
Inferior to CT			CT gave only fair relief
		None	
		None	
Inferior to aminophylline	None	None	
		None	
		None	
		None	
Slightly inferior to both PBZ and CT	None	None	Satistfactory relief; less complete than PBZ or CT but produced no drowsiness as others did
Superior to CT		None	
		None	Urticaria of undetermined origin; patient did not return after initial report of marked efficacy

The eighty-two patients exhibited a total of eighty-nine specific allergic disorders which were active at the time of observation, permitting evaluation of clinical effects. In addition, twelve patients were known to have had asthma in the past; no symptoms referable to the lower respiratory tract were present during the period of study, and these patients have been evaluated for the response of other allergic complaints only, usually nasal. Another patient had a questionable history of angioneurotic edema but was evaluated only for active nasal complaints.

The medication was administered either in regular 4 mg. tablets every four hours or as the need arose or as Extentabs, 12 mg. tablets, administered at eight-hour intervals or as the need arose. Patient 7 took 8 mg. of the regular form every four hours and Patient 9 took an Extentab every three hours; the former experienced heartburn on a few occasions whereas the latter showed no ill effects. When possible, individual patients were alternated on both forms of the drug in order to compare relative efficacy and preference. Patients had been maintained on Dimetane for periods varying from one week to six months at the time the data were summarized; many of the patients who reported favorable results have since been maintained on the drug for much longer periods. Throughout the period of study, patients were questioned carefully to elicit untoward side effects and, where possible, therapy with other established antihistaminic agents was alternated with the use of Dimetane; in some instances alternation was carried out several times in an individual patient.

A summary of our experience with this group of patients is presented in Table I.

THERAPEUTIC RESULTS

Table II summarizes the effectiveness of Dimetane in the various allergic disorders studied. Results have been classed as excellent (complete and long-lasting relief), good (substantial relief with residual mild complaints), moderate (significant improvement but with substantial residual complaints), and slight or no relief. The first two categories comprise the clinically satisfactory results. However, it should be noted that the group of cases exhibiting "moderate relief" represents significant though inadequate improvement.

TABLE II. RESPONSE TO DIMETANE IN VARIOUS ALLERGIC DISORDERS

DISORDER	EXCELLENT		GOOD		MODERATE		SLIGHT TO NONE		INDETERMINATE	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Vasomotor rhinitis	15	25.8	20	34.5	12	20.6	11	19.1		
Hay fever	6	30.0	6	30.0	2	10.0	6	30.0		
Angioneurotic edema or urticaria			3	60.0	2	40.0				
Bronchial asthma					1	25.0	3	75.0		
Allergic cephalalgia									1	100.0
Allergic bronchitis			1	100.0						
Total	21	23.6	30	32.5	17	21.5	20	22.0		

Some of the patients in this group obtained more relief from Dimetane than from other antihistaminics, and some observers undoubtedly would include this group in the therapeutically active classification. We have preferred to omit that group in evaluating our clinically satisfactory results. It is noted that over-all results for eighty-nine allergic disorders (in eighty-two patients) were satisfactory in 56.1 per cent. When the various allergic disorders are considered individually, it is noted that the most effective responses were achieved in patients with vasomotor rhinitis and hay fever, with satisfactory results in 60.3 per cent and 60.0 per cent, respectively, of the patients studied. In the small group with angioneurotic edema or urticaria, good results were obtained in 60 per cent of the patients. One patient with allergic bronchitis reported good results. No significant responses were secured in any of the four asthmatic patients, a finding in keeping with the recognized ineffectiveness of antihistamines in this disorder. The results were indeterminate in one patient believed to suffer from allergic cephalalgia.

The actual percentages do not completely indicate the clinical situation. This is borne out below by comparison with other antihistaminics according to the criteria set forth above. Table I notes several examples of poor or absent response to Dimetane in patients who likewise failed to respond to any form of therapy, including other antihistaminics, and the reader is also referred to the comment in the preceding paragraph pertaining to the group of "moderate" responses.

COMPARISON WITH OTHER ANTIHISTAMINICS

Table III summarizes the results obtained by alternating Dimetane with various accepted antihistaminic agents. As indicated in Table I, there were several instances of tolerance which resulted in a seesawing when agents were compared, Dimetane at first exhibiting more effectiveness, to be supplanted at a later period by another antihistaminic, or the reverse occurring. In such

TABLE III. EFFECTIVENESS OF DIMETANE COMPARED WITH OTHER ANTIHISTAMINIC AGENTS

OTHER AGENTS	DIMETANE SUPERIOR	DIMETANE EQUIVALENT	DIMETANE INFERIOR
Pyribenzamine	13	10	2
Chlor-Trimeton	16	8	8
Thephorin	1		

instances, each drug was listed in the table as superior on one occasion. In most instances, when more than one period of alteration was carried out, the superiority of a given agent was constant. It is noted that thirteen patients preferred Dimetane to Pyribenzamine, ten noted similar results with both agents, and two patients preferred Pyribenzamine. Sixteen patients reported superior results with Dimetane when compared with Chlor-Trimeton, eight found both agents to be equally effective, and eight preferred Chlor-Trimeton. In one instance Dimetane afforded more relief than Thephorin. One patient with asthma received moderate relief from aminophylline but none with Dimetane.

COMPARISON OF REGULAR TABLETS AND EXTENTABS

In twenty-nine instances it was possible to compare the effectiveness of the two forms of the drug. Of this group, 51.7 per cent preferred the Extentabs as offering more complete and persistent relief while 24.2 per cent obtained better results with the regular tablet (Table IV).

TABLE IV. PREFERENCE FOR TYPE OF TABLET

TABLET	NUMBER OF PATIENTS	PER CENT
Regular tablet	7	24.2
Extentabs	15	51.7
No preference	7	24.2

DEVELOPMENT OF TOLERANCE

Four patients exhibited development of tolerance to the drug. While it is not possible to rule out spontaneous increase in severity of the active disease state as the cause of "tolerance," it is of interest to note that three of the four patients demonstrated similar tolerance to various other antihistaminic agents. It might be speculated that the development of tolerance in these instances is a function of the patient rather than of the drug per se and represents an atypical response. Vaughan[1] has noted a similar phenomenon in some of his patients and has drawn a similar conclusion regarding the mechanism of tolerance to antihistaminics.

TOXICITY

One patient experienced heartburn on one or two occasions only. Another patient developed a macular eruption of the arms while on Dimetane; this disappeared three days after the drug was discontinued. There was no change in the peripheral blood. Five patients complained of drowsiness; in most instances, this was mild but two patients discontinued the medication because of this reaction. Reference to Table I will show that this prominent side effect of many antihistaminic agents was a very slight problem with Dimetane, and contributed significantly to its clinical effectiveness. In several instances, patients expressed preference for Dimetane in comparison with other antihistaminics, even though the actual relief of symptoms was not greater with Dimetane; in such cases, the absence of annoying drowsiness was a decisive factor in shaping the patient's choice. Patient 80 expressed preference for Dimetane because of the absence of side effects, although actually more relief of the angioneurotic edema was obtained with either Pyribenzamine or Chlor-Trimeton.

The low incidence of toxicity in the dose levels employed in this study suggests that considerably larger doses might be tolerated in many instances; this would enhance the degree of effectiveness in patients in whom some effect has been obtained on smaller doses, and it might achieve significant results in the group of previously nonresponsive patients.

DISCUSSION

Chemically, all antihistaminics are derived from ethylenediamine ($NH_2CH_2CH_2NH_2$), from hydroxyethyleneamine ($HOCH_2CH_2NH_2$), or from propylamine ($CH_3CH_2CH_2NH_2$). Dimetane falls into the last group. The pharmacology of Dimetane has been studied by Hotovy and Roesch,[2] who reported that the drug possessed potent antiallergic qualities and was relatively nonhypnotic and well tolerated. Sixty per cent of a group of guinea pigs were protected from asthma customarily induced by intravenous histamine. As in the cases of other antihistaminic agents, an analgesic effect was noted in the test animals. A large therapeutic range was observed.

There have been several clinical reports in the German literature. The German clinicians have used a timed release preparation called "duplettes" in which the outer layer containing 9 mg. of the compound is released rapidly and an inner core of 7 mg. is released over a period of several hours. A 2 per cent ointment has been used in the treatment of skin conditions. Weyer[3] treated 262 patients with a variety of skin disorders with both local and oral therapy. Good effects were reported in the acute cases, particularly those suffering from urticaria, drug rashes, local eczema, and generalized dermatitis. Results were less satisfactory in chronic skin disorders. Tolerance was good, and hypnotic effects were present in only 7 per cent of the cases, a situation which Weyer feels is particularly beneficial in cases treated on an ambulatory basis. Three patients exhibited some degree of excitement while receiving the drug.

Wawersig[4] treated 100 patients who exhibited pruritus due to a variety of local and general disorders. He reported excellent results in 45 per cent of the cases and good results in 35 per cent of the patients, with only 20 per cent not responding. His paper does not detail the pathology of the various disorders treated with the antihistaminic. He comments, too, on the absence of significant side effects, although two or three of his patients had mild gastrointestinal complaints which might have been due to the drug.

Shirrin and Schulz[5] found that of eighty-nine patients suffering from "serious dermatitis, urticaria, Quincke edema and hay fever" (the breakdown is not more detailed than this), seventy-eight showed good results and only two failed to respond. Of twelve patients with chronic skin disorders, itching was relieved in seven, but to a very limited degree. They concluded from animal experiments and clinical observations that Dimetane is "comparable to the active antihistaminics which are presently known," and they commented on the lack of hypnotic and gastrointestinal side effects.

In this country, Thomas[6] has recently reported on the use of Dimetane in 140 patients with various allergic disorders. One hundred and twenty-two members of the group showed satisfactory results. The results were best in the group of patients with angioneurotic edema and urticaria, rhinitis and asthma, and hay fever and asthma. The results were least satisfactory in the patients suffering from perennial allergic rhinitis; only six of the ten

patients reported adequate responses. Seventeen patients who had previously been unable to tolerate other antihistaminics showed no ill effects from Dimetane, whereas eight patients were unable to tolerate Dimetane but had no side effects when on other antihistaminics. Sixty-three patients preferred Dimetane to other antihistaminic agents; nine preferred other antihistaminics. Thomas reports that only eleven patients could not tolerate the agent, the chief complaint being drowsiness. Of this small group, only eight patients had complaints severe enough to warrant interruption of therapy and five of these were unable to tolerate any antihistaminic.

Dr. Horstman[7] has observed a series of sixty-eight patients treated with Dimetane. Thirty of thirty-four patients with pollen hay fever reported excellent to moderate results, and twenty of twenty-two patients with perennial allergic rhinitis obtained similar good results. Ten of twelve patients with chronic recurrent urticaria responded well. Sixty per cent of the patients who had also taken other antihistaminics preferred Dimetane.

At the time this report was written, 1,877 patients[8] had been studied in this country by a total of ninty-three investigators, with excellent and good results in 80.4 per cent of the cases, fair results in 8.5 per cent, and no results in 8.3 per cent. Drowsiness was reported in 6.6 per cent of the patients and other side effects in 2.0 per cent.

Our own results indicate a somewhat lower rate of effectiveness, averaging 56.1 per cent for the over-all series of eighty-two patients exhibiting eighty-nine allergic disorders, with the best results noted in the vasomotor rhinitis and hay fever groups (60.3 per cent and 60.0 per cent, respectively). Sixty per cent of a small group of patients with urticaria or angioneurotic edema showed good responses. However, if our "moderate" responses are included, then the totals rise to 80.9 per cent and 70 per cent, respectively, for the vasomotor rhinitis and hay fever groups showing a therapeutic response. These figures coincide fairly close with those reported by other investigators. Only 6 per cent of our patients exhibited drowsiness, a figure that again compares closely with those of other investigators. Only two other patients demonstrated side effects, one gastrointestinal and one dermatologic. The lack of hypnotic reactions has been very striking in this study and has been an important consideration in evaluation of the drug's usefulness.

These results would indicate that Dimetane is a potent and useful antihistaminic agent whose low incidence of side effects should help it find a valued place in the therapy of the ambulatory allergic patient. The rather marked variability in responsiveness to a given agent by the individual allergic patient and the small group of patients who seem to develop tolerance to all antihistaminics rapidly are clinical situations that should ensure interest in a new antihistaminic, even though a large number of potent and satisfactory drugs are already available to the clinician.

SUMMARY

1. Dimetane is a highly effective antihistaminic agent in those allergic disorders in which antihistamines have been shown to possess usefulness.

2. The low incidence of side effects, coupled with the infrequent development of tolerance, enhances its therapeutic value. The low incidence of the hypnotic effect makes Dimetane especially useful for the ambulatory allergic patient.

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ENHANCEMENT OF HISTAMINE AND ANAPHYLACTIC SHOCK IN MICE BY BRUCELLA ABORTUS

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AN INCREASE in susceptibility to histamine[1] and to anaphylactic sensitization[2] has been observed following the inoculation of white mice with a vaccine of *Hemophilus pertussis* phase I organisms. Experimental infection with *H. pertussis*,[3] the establishment of sarcoma 180,[4] increasing age of the animal,[5] and treatment with a vaccine of *Brucella abortus* organisms[6] all result in an altered reactivity to histamine also. However, most experimental agents and conditions[6, 7] which have been described for the mouse have no effect on the inherent resistance of this animal to histamine. On the other hand, although many diverse substances have been found capable of enhancing the anaphylactic sensitivity,[8] it should be noted that a parallel increase in susceptibility to histamine does not result. In addition to *H. pertussis* and certain fractions obtained therefrom,[9] only *B. abortus* has been found capable of significantly altering histamine and anaphylactic sensitization.

In contradistinction to the above findings with *B. abortus*, Abernathy and Spink[10] reported that in their hands neither *B. abortus* nor other strains of brucellae had the capability of decreasing the resistance of the white mouse to histamine. Since the results obtained in our previous study[6] were apparently significant, it was deemed of interest to reinvestigate and augment the experimental criteria of these studies. It should be emphasized at the outset that the capabilities of *B. abortus* for altering these sensitivities, although significant, are far less than those of *H. pertussis*.[6]

MATERIALS AND METHODS

Mice.—Female white mice of the Swiss-Webster strain were purchased from Tumblebrook Farm. We have used this strain of mouse in almost all of our previous studies. At the start of the experiment each mouse weighed about 18 to 20 grams.

B. abortus Vaccine.—We are indebted to Dr. R. V. Johnston of Pittman-Moore Company, Indianapolis, Indiana, for a generous quantity of vaccine. Each vial of *Brucella abortus* vaccine, desiccated, contained approximately 6×10^{10} viable cells of the attenuated strain No. 19. Immediately prior to use the contents of each vial were reconstituted with either 0.85 per cent saline

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containing Merthiolate 1:10,000 or Coca's fluid. The lipopolysaccharide from *B. abortus* used in some of the experiments was provided through the courtesy of Dr. C. W. Christensen of Difco Laboratories, Inc., Detroit, Michigan.

Sensitization.—Each mouse was given an intraperitoneal (i.p.) inoculation of 0.5 ml. of a mixture containing *B. abortus* vaccine (2×10^9 cells) or the lipopolysaccharide (100 or 200 mcg.) and a heterologous protein antigen, either 1 mg. of recrystallized egg albumin (EA) or 0.03 ml. of horse serum (HS).

Histamine Sensitivity.—On the fourth day after immunization, each mouse received an i.p. inoculation of histamine as the phosphate salt, 36 mcg./gram mouse. This amount of histamine corresponds to approximately the $L.D._{100}$ for mice treated with *H. pertussis.* Although all mice showed some reaction, the actual result is recorded as mortality (number of mice dead/number of mice injected).

Anaphylactic Sensitivity.—On the tenth, fifteenth, or twentieth day following the initial treatment with brucella, an intravenous inoculation of homologous antigen, 1 mg. EA or 0.1 ml. HS, was given each mouse. Reactions other than actual death were disregarded in the final tabulation, with the mortality results expressed as number of animals dead per number of animals challenged.

RESULTS AND DISCUSSION

Our previous conclusions[6] indicating that pretreatment with *B. abortus* enhances the reactivity of the mouse to the lethal effects of histamine have been confirmed. As can be seen from the data in Table I, a mortality of about 50 per cent was obtained. This value is of statistical significance. We have previously noted[6] that the degree of sensitivity obtained with *B. abortus* was not as great as that produced by *H. pertussis,* as the 95 per cent mortality obtained for the latter in these experiments will indicate.

TABLE I. EFFECT OF BRUCELLA ABORTUS ON HISTAMINE SENSITIVITY

		SENSITIZING AGENT				
DAY	CHALLENGE AGENT	B. ABORTUS 2×10^9 CELLS	HEATED B. ABORTUS 2×10^9 CELLS	H. PERTUSSIS 6×10^9 CELLS	LIPOPOLYSACCHARIDE B. ABORTUS 200 MCG.	UNVACCINATED CONTROL
4	Histamine phosphate 36 mcg./Gm. mouse i.p.	42/83*	5/45	18/19	8/34	0/20

*Denotes number of animals dead per number of animals challenged.

In the above experiments inactivation of *B. abortus* was produced with phenol or Merthiolate. The failure that Abernathy and Spink[10] reported may be attributed to their technique, in which heat-killed *B. abortus* organisms were used as the sensitizing medium. Maitland and colleagues[11] have reported that the factor responsible for histamine sensitization in *H. pertussis* is inactivated completely when heated at 80 degrees for thirty minutes. Confirmation was extended by Kind[12] who, although he did not find complete inactivation, did observe a reduction in histamine-sensitizing ability following heating. In an attempt to duplicate more closely the technique of Abernathy and Spink,[10] a

subsequent study was carried out using heat-killed organisms obtained by autoclaving for thirty minutes at 15 lbs. pressure a saline-reconstituted suspension of *B. abortus*. As can be seen, the mortality obtained by prior sensitization with these heat-killed cells was only about 10 per cent, thus confirming the effects of heating on the sensitizing properties.

Since relatively few extraneous agents have the ability to decrease the tolerance of the mouse to histamine, a certain degree of specificity must be recognized. It has been noted that *H. influenzae*,[6] *H. pertussis* phase IV,[7] and certain other unrelated vaccines[6] do not possess the histamine-sensitizing property. The failure to produce an increased sensitivity with *B. melitensis*, *B. suis*, or active infection with *B. melitensis* as reported by Abernathy and Spink[10] should, therefore, not have been entirely unexpected. With reference to the strain difference that exists between mice with respect to ability to sensitize to histamine, it should be indicated that this has been amply demonstrated.[13, 14]

The observation that prior treatment of the mouse with a lipopolysaccharide obtained from *B. abortus* produces a decreased tolerance to histamine (Table I) also is of considerable interest. It should be recalled that an increased sensitivity to histamine could not be demonstrated by us[8] using the protein nucleate of *B. abortus*, or by Abernathy and Spink,[10] using brucella endotoxin.

TABLE II. EFFECT OF BRUCELLA ABORTUS ON ANAPHYLACTIC SENSITIZATION TO HORSE SERUM AND EGG ALBUMIN

		SENSITIZING AGENT								
		B. ABORTUS 2×10^9 CELLS		HEATED B. ABORTUS 2×10^9 CELLS	H. PERTUSSIS 6×10^9 CELLS	LIPOPOLYSACCHARIDE B. ABORTUS (EA)		UNVACCINATED CONTROL	
DAY	CHALLENGE AGENT	HS	EA	HS	HS	100 MCG.	200 MCG.	HS	EA
10	HS 0.1 ml. i.v.	2/62*		1/38	14/14			0/15	
	EA 1 mg. i.v.		0/24			14/15	20/33		0/20
15	HS 0.1 ml. i.v.	11/55		4/47				3/66	
	EA 1 mg. i.v.		5/10						
20	HS 0.1 ml. i.v.	2/21							
	EA 1 mg. i.v.		0/20						

*Denotes number of animals dead per number of animals challenged.

The capability of *B. abortus* to enhance anaphylactic sensitization in the white mouse was re-evaluated and confirmed our previous observations.[6] The results are shown in Table II. Sensitization seems to reach a maximum at about the fifteenth day and subsequently decreases rapidly. Using *H. pertussis* as the sensitizing organism, our experience has shown that the height of anaphylactic sensitivity is reached at about the tenth day and persists at a

maximum for an additional ten days. These differences, together with the lower incidence of mortality obtained with *B. abortus,* further emphasize that the latter is not as potent a conditioner to sensitization as is *H. pertussis.*

It is of interest that the lipopolysaccharide of *B. abortus* enhances anaphylactic sensitization. At the 200 mcg. level a mortality of about 60 per cent was obtained by the tenth day, while at the 100 mcg. level a 93 per cent mortality was attained. The difference in mortality at the two levels may be partly the effect of the toxicity of the lipopolysaccharide; at the higher dosage levels the mice became toxic, with many deaths resulting following inoculation with the polysaccharide. The decreased incidence of mortality following challenge may perhaps be a reflection of the stress phenomenon. The isolation of a nonparticulate, soluble fraction which enhances sensitivity offers a valuable tool for furtherance of the investigation into the mechanisms involved.

SUMMARY

The ability of *Brucella abortus* organisms to alter the sensitivity of the white mouse to the lethal effects of histamine has been confirmed. It has been shown that heating has the effect of decreasing this property. Anaphylactic sensitization is also diminished by heating. The lipopolysaccharide obtained from *B. abortus* was also observed to have the capability of sensitizing the white mouse to the lethal effects of histamine and protein antigens.

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IS INTRINSIC ASTHMA A REVERSIBLE DISEASE?

A Follow-up Study

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IF ASTHMA is a reversible disease—if treatment directed toward the exciting cause can bring about a true cure—then one can be satisfied with the idea that this exciting cause can explain the whole disease. If, on the other hand, the disease is not reversible—if the symptoms tend to recur and especially if they recur from different exciting causes—then one must look for some other factor in addition to the exciting cause.

A group of 272 patients with intrinsic asthma seen in private practice has been followed for a minimum of fifteen years, and many for a much longer time (up to twenty-five or thirty years). The gross results are shown in Table I. The numbers are small because, first the selection of cases is restricted to those patients whose asthma was intrinsic (that is, it was due to some factor which the patient carried within himself at all times and in all places) and, second, these patients had to be known for at least fifteen years.

Only 59 patients, or 21.7 per cent of the total, have become cleared of asthma, but they represent the most interesting group. Their clearance suggests that the process is reversible and that, in their cases at least, the exciting cause (usually an infection) and its effects did, in fact, constitute the whole disease. That such an easy conclusion is not correct is shown by the subsequent histories, for in a number of cases the asthma has recurred even though there was a free interval of as long as twenty years between the two attacks. The study shows well the importance of following these patients for a long time.

In this study, the progress of each patient has been plotted on a series of charts, and three of the charts are shown herewith. Each patient is represented by a line which begins at the age of onset. *X* marks the age at first visit, and the line continues in dashes—longer for bad attacks, shorter for milder episodes. *C* indicates the age at clearance ("cure" is too strong a word, as will be seen later), and this *C* is followed by a dotted line until a new *C* indicates a further report that all is well or until an upright mark indicates a return of asthma. *S* means sinus operation. Initials at the left, when underlined, represent male patients. One or two words on each line suggest the treatment or the change that was presumed to be responsible for clearance of the asthma.

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TABLE I. INTRINSIC ASTHMA—FOLLOW-UP OF 272 PATIENTS

	NUMBER AND PER CENT	WOMEN	TOTAL DEAD	DEAD OF ASTHMA
Cleared	59 (21.7%)	45 (76%)	5	0
Improved	119 (43.7%)	84 (70%)	22	0
Unimproved	94 (34.5%)	52 (55%)	41	7
Total	272 (100%)	181 (66%)	68	7

Fig. 1 shows the fifteen patients whose skin tests were positive to house dust and other substances, but in whom the clearance of asthma had nothing to do with allergy. No recognized changes were made in their environment or diet, and they had not been desensitized to anything. The ages at onset range from the twenties to the sixties. The chart shows seven men and eight women; the sexes are represented equally.

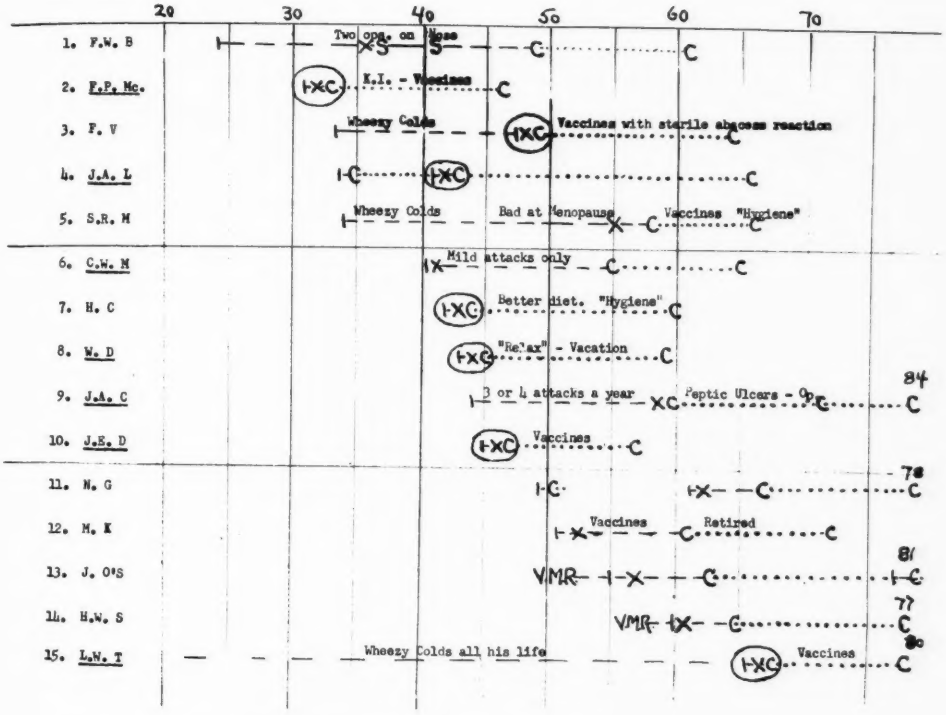

Fig. 1.—Intrinsic asthma, skin tests positive, "cured."

Key to Symbols: Each line represents a patient; the line begins at the onset of asthma. *X* marks the age at first visit. The dashes indicate attacks of asthma. *C* means clearance of asthma and is followed by a dotted line until a new *C* indicates a new follow-up (that the patient is still clear) or until an upright line indicates that the asthma has recurred. *S* means sinus operation. In Fig. 3 some lines end with solid hearts, meaning coronary disease, or with open hearts, meaning cor pulmonale. *A* means death from asthma. *D* means death from unknown cause. *P* means pneumonia. V.M.R. means vasomotor rhinitis which preceded the asthma.

Fig. 2 is analogous. It shows the first fifteen—the youngest at onset—of the forty-four patients whose skin tests were negative and whose asthma has cleared away. Allergy was not a factor. One could say that the girl athlete in Case 1,

who was relieved of asthma at the time of her marriage, had moved to a new home and thus had escaped from a dust which had been causing trouble in the old place and that, therefore, her asthma was of extrinsic origin. The fact is, however, that her story as a whole shows well that her asthma disappeared because her marriage gave her the peace and security which she badly needed. Her case illustrates well the difficulties and pitfalls of classification. Even if the outcome is known and the kind of treatment given is known, it is still hard to be sure that the true exciting cause is identified.

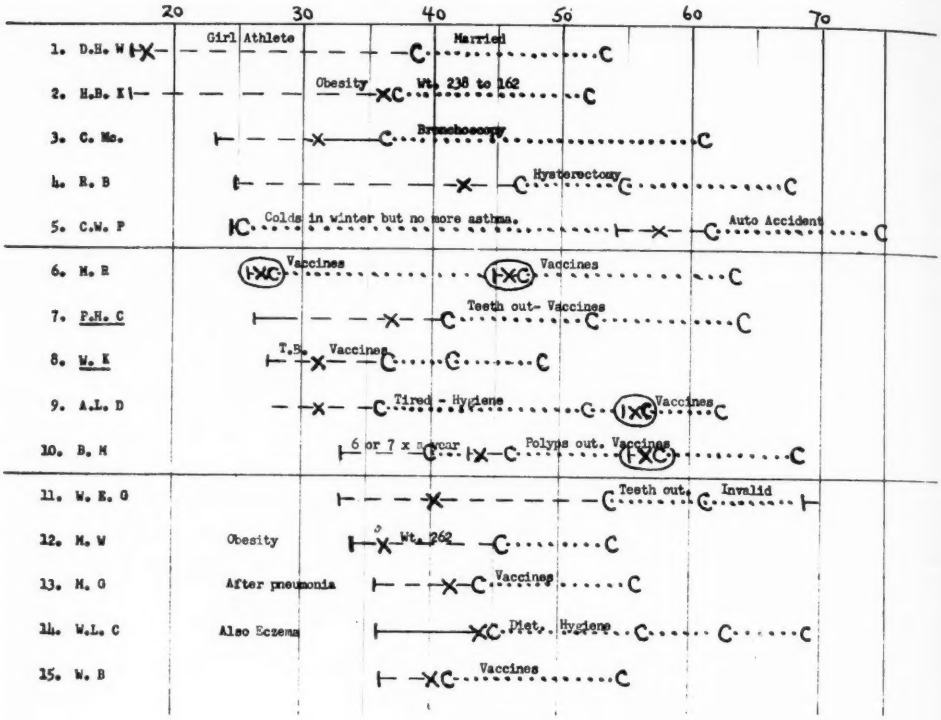

Fig. 2.—Intrinsic asthma, tests negative, "cured." *(For Key to Symbols, see Fig. 1.)*

In most of the intrinsic cases the asthma began with an infection. "I had a cold" or "the asthma began after bronchitis" or even "after pneumonia" are the common reports about the onset, and in many of the cases treatment with potassium iodide and vaccines aimed at the infection was followed by improvement. The exact percentage of infectious causes cannot be given, for other factors appear to confuse the picture in almost every case. One woman was too fat. Another was "always tired" and felt much better when she learned how to take better care of herself, that is, when she learned the principles of good "hygiene" for both her body and her soul. In other cases the difficulty was psychogenic; the asthma cleared when "troubles at home" were relieved or when the job was changed to a more pleasant environment. Finally, in some cases

clearance of asthma came even though there was no obvious explanation for the happy outcome. These last categories were not common, making together not over 10 or 15 per cent of the whole group.

Several interesting observations are revealed by the charts. The first is that in a number of cases the onset, the first visit, and the clearance came close together to indicate a short, even if sometimes severe, disease lasting not over two or three years. In this modern day, when cortisone is used so freely, one should note that fifteen or twenty years ago, before cortisone was discovered, some patients recovered quite promptly under ordinary treatment.

The method of treatment varied widely. Injections of stock vaccines have been given to many patients, and in a number of cases these treatments are effective—so much so that this effect of stock vaccines needs much more study. For example, how does this nonspecific therapy compare with the effect of injections of extracts of dust, of feathers, or of pollen? Meantime, clearance did not always follow the first treatment. As some of the lines show, there might be an interval of three, four, or five years between the time of treatment and the time of relief. The effect was not always direct.

Paranasal sinusitis was found in six of these cleared patients. Polyps had been removed in three. Sinus operations were made in one. In four cases, clearance followed the removal of abscessed teeth. Other "treatment" included the effect of other surgical operations and an automobile accident. Two patients were cleared when their remarkable obesity was controlled. Psychogenic factors turned out to be of primary importance in five cases.

The second important observation shown by the charts is that in at least six patients the asthma recurred after a long period of freedom, and in three of these the new attack yielded again, and promptly, to treatment with vaccines and potassium iodide. These recurrences show well that the word "cure" cannot be used. Also, they show that a basic mechanism of some kind is still operative.

Only about one-fifth of the cases are cleared. The others have been divided into these 119 patients whose asthma is improved (43.7 per cent of the total series) and the ninety-four patients (34.5 per cent) who are still in trouble, that is, whose asthma is unimproved.

Those in the improved group have learned to control the symptoms and can carry on a normal life, even though they wheeze at times and must keep the nebulizer or the pills within easy reach. The various factors in their cases have been quite comparable to those in the cleared group. Some of them have become entirely clear for a year or two at a time, and these interludes could be traced to the relief of the stress, physical or emotional, which was holding them down.

Paranasal sinusitis was much more common here than in the cleared cases. It was found in a total of forty-three, or 36.1 per cent, of the 119 patients, that is, in more than one-third of the cases. Nasal polyps were found and removed in thirty-one cases, and radical sinus operations were made in eight cases, with benefit which was temporary at best.

Twenty-two of the improved patients have died of heart disease, cancer, or pneumonia (all from "natural causes"). None have died of asthma.

Fig. 3 shows a sample of the ninety-four patients—one-third of the total series—whose asthma is unimproved. This, of course, is the over-all, long-term appraisal. It does not mean that symptomatic treatment was never effective,

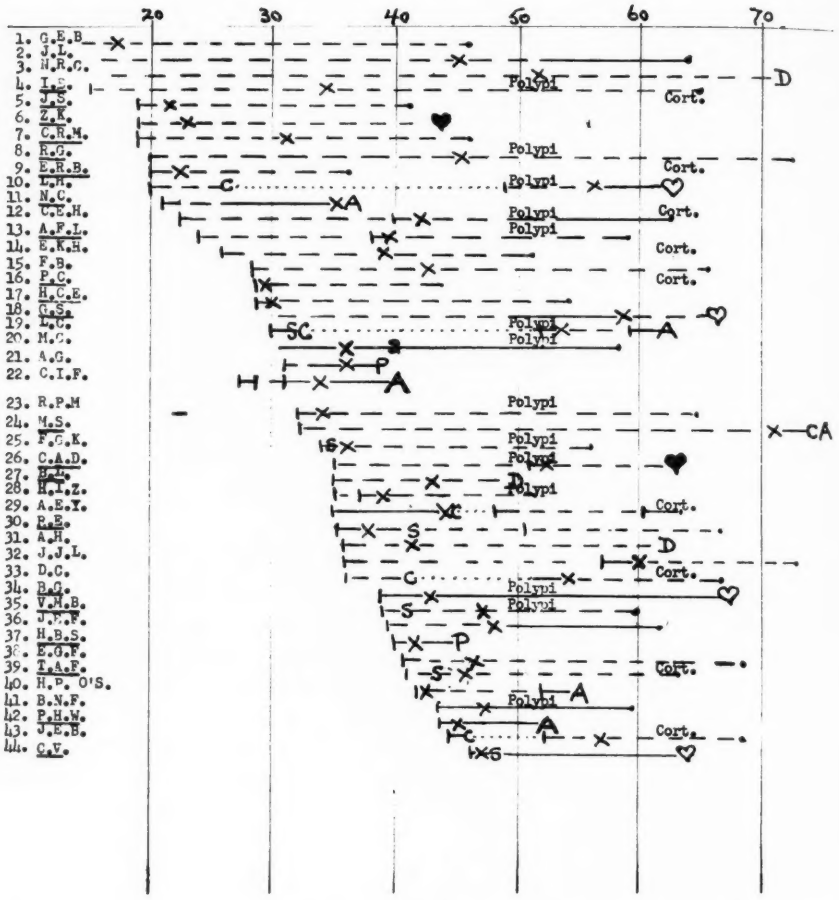

Fig. 3.—Intrinsic asthma, unrelieved (skin tests negative). (*For Key to Symbols, see Fig 1.*)

at least for a time. Skin tests were positive in twenty-nine patients but, as in the cleared group, there was no evidence in the history or in the course of the asthma to indicate that the corresponding foreign substance was concerned with the symptoms. Even in these bad cases there were at least four patients whose asthma had been cleared for intervals of two or three years. Asthma is not always a persistent, relentless process.

Sinusitis is common here; it was found in thirty-seven cases, which is 39.3 per cent of the unimproved group. Nasal polyps were found in twenty-seven

cases, and sinus operations were performed in fifteen of the thirty-seven cases (only three of the patients had polyps later). Cortisone is being given to five patients at this time, fifteen years after the original study.

Forty-one of these unimproved patients have died, mostly from "natural causes." At least seven died of asthma, however, after a long, severe struggle. Fig. 3 shows five of these deaths from asthma—the asthma cases numbered 11, 19, 22, 40, and 42. At autopsy one of them (Case 22) showed the typical findings of periarteritis nodosa. Autopsies were not made in all seven cases; the diagnosis of death from asthma was considered as probable according to the account in the last report. Cor pulmonale, represented by the open hearts in Fig. 3, was the likely cause of death in four other cases; the asthma in this group continued in severe form up to the end of life.

Later in the course, corticoid drugs were used in nine cases, and one can expect that henceforth these old experiences with severe asthma will not have to be repeated.

DISCUSSION

This study shows that, whereas the symptoms of asthma can be controlled by relatively simple means in a majority of the cases (the cleared and the improved groups make up 65 per cent of the total), there remains about 35 per cent in which the asthma is a severe disease which was hard to treat before cortisone was discovered.

What is wrong with these difficult cases? The theory of allergy as a reaction to dusts, foods, or drugs does not make sense with the clinical histories. The asthma does not clear in the clean environment of the hospital even in the oxygen tent.

Infection is important, since most of the attacks begin with new colds. Can infection account for the whole disease? Can one explain the persistence of asthma for thirty years, from the age of 20 or 30 up to the age of 50 or 60, on the basis of a chronic infection with various coccus organisms? Counts of the white blood cells, the proportion of polynuclears, and the sedimentation rates, are not often increased; these patients do not show the earmarks of a chronic infectious process. It is true that in one or two cases the removal of bad teeth or drainage of the sinuses has brought relief, but one of the interesting findings in this study is that in most cases the improvement after sinus operations does not persist for very long. Another point is the relationship between the incidence of sinusitis and polyp formation and the severity of the asthma. In the cleared group, sinusitis occurred in only 11.8 per cent of the cases, whereas it was found in 39.3 per cent of the unimproved cases. This is further evidence that paranasal sinusitis is a part of the picture of asthma, especially of severe asthma.

Psychogenic factors play some part in every case of asthma, since most patients feel better when they can understand their disease and can learn what they can do to control the symptoms, but these factors are primary in only a few patients. One can say that "stress and strain—physical and emotional" is a catch phrase that makes sense with the clinical histories.

How do these many different exciting causes produce the symptoms? Present theory says that any one of them can release an effector substance normally present in various cells and tissues in the body, and we learn about histamine, acetyl choline, and now serotonin. So far, however, no one of the particular substances has been found to produce effects which are good enough to explain the whole picture. The idea, however, is reasonable, and one can hope that new researches will show that these effectors, or others like them, can be held accountable. Meanwhile, the same old question comes up again: "How did the patient get that way in the first place?" The answer is still unknown.

This article shows what happens to patients with chronic asthma during fifteen years or more after the original examination. The fact that about two out of three have been improved, so that their asthma is under good control, is encouraging, especially as this group includes 20 per cent of the whole who have become cleared of asthma, at least for a time.

Meanwhile, a more careful study of the progress of the cases reveals at least two which are of special interest. Fig. 3 includes their outlines. Case 10 (L. H.), at the age of 20, had the grippe and developed asthma. At the age of 26 she moved to another town, and the asthma cleared. For twenty years she was well, and then when she was 48 years old a bad cold was followed by asthma again. This asthma was severe; nasal polyps formed, and finally at 63 she died "after a year's invalidism due to asthma." Her death was due to a failure of the right heart, probably.

In Case 19 (L. C.) asthma began at the age of 30. The patient had a sinus operation at 32 years of age but she changed her job at the same time. After that she had no more asthma for twenty years, until she was 52. Her job entailed exposure to chlorine fumes and the early asthma was due to allergy, probably. This new asthma, which appeared at age 52, began with pneumonia. It was more severe. It was complicated, as before, by sinusitis and polyps, and again it persisted. Some years later came the note: "Mrs. L. C. passed away (at age 63) from bronchial asthma."

The point is that in these two cases the first episode of asthma was due, evidently, to a cause which was allergic (extrinsic) in nature, while the second episode twenty years later was excited by a different cause; it was intrinsic. The two kinds of asthma have occurred in the same patient, and that is a very important observation. If other cases with the two kinds of asthma coming in sequence can be identified, then one must consider that the basic lesion is a defect of some kind which becomes manifest when allergy or infection, or perhaps a psychogenic factor, pulls the trigger. Some day someone will explain how and why the gun is loaded.

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ASTHMA IS A CONSTITUTIONAL DISEASE

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IN A recent follow-up study of 272 patients with intrinsic asthma,[1] two of these patients were of particular interest for at different times they had suffered from two kinds of asthma. In their teens and twenties the exciting cause of their symptoms was extrinsic; they were allergic. In one patient the asthma cleared when, at the age of 26, she married and moved to another town, so that she escaped from a dust that was causing trouble at home. In the other the asthma cleared when she changed her job and thus escaped from the fumes of chlorine in the chemical industry. After recovery both of these women remained well for twenty years, and then asthma developed again—in one after a bad cold at the ago of 48, and in the other after frank pneumonia at the age of 52. In both cases this recurrence was severe, and the asthma continued until both patients died at the age of 63, one of asthma and the other of cor pulmonale.

Further study of records of old patients, aided by the receipt of belated answers to a questionnaire, has revealed eighteen additional cases in which each patient had suffered from two kinds of asthma. In each case the history showed two well-defined episodes separated by clear intervals which lasted from eight to thirty years. This, I believe, is an important finding, for it shows that the exciting cause of the attacks of asthma does not constitute the whole disease. The symptom, asthma, may be produced by allergic reactions to animal danders, pollen, or household dusts, and it may be produced by infections, either acute or chronic; it can also be produced by psychogenic disturbances. When it is possible to demonstrate two different exciting causes occurring in sequence in the same patient, it becomes quite clear that no one of these causes is sufficient by itself to explain the whole process.

Fig. 1 shows a summary of the eighteen cases. Each case is represented by a line which begins at the age at onset in early life. The line is interrupted to denote the free interval and then it begins again with the new onset at the age of 30 or 40. The character of the asthma is indicated roughly by dashes to suggest attacks or by solid lines to mark more persistent asthma. *X* indicates the patient's age at the time of the first visit. *C* denotes clearance of asthma and is followed by dots until a new *C* indicates another report that all is well or until an upright mark indicates a recurrence. *S* means sinus operation. *A* indicates death from asthma, and the solid heart represents death from coronary disease.

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As shown in the recent follow-up study, the close time relationship of onset, visit, and clearance in some of the cases (Nos. 9, 12, 13, and perhaps 16) indicates that asthma can be a short and severe disease. Incidentally, this point serves as a control for the results of the use of cortisone and its relatives in modern treatment. It shows that some patients can do well without cortisone.

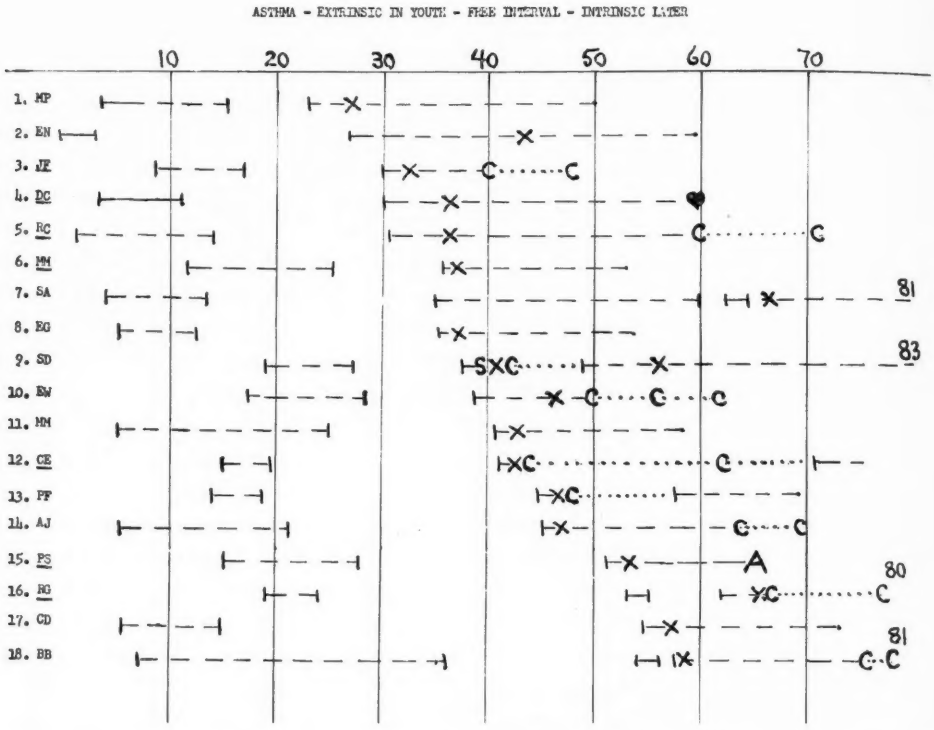

Fig. 1.—Each horizontal line represents one of the eighteen patients. The continuous line and the dashes suggest roughly the severity and persistence of the asthma. Initials underlined are those of men. In each of these cases the line is interrupted to show the ages at which the asthma of the first episode subsided and the second episode began. *X* indicates the age at the time of the first study. *C* represents clearance of asthma, and the dotted line shows the duration of that clear period until a new *C* reports that all is well or until an upright mark indicates a recurrence of asthma. *S* stands for sinus operation. *A* denotes death from asthma, and the solid heart represents coronary disease.

Table I shows the exciting causes of the episodes in the same eighteen patients. The figures indicate the ages at which episodes or free intervals began and ended.

Skin tests observed at the time of the visit in the second episode were positive to one common dust and food substance or another in all but four of the eighteen cases. The early asthma was due to allergy. Half of the patients in this little group were skin-test-sensitive to animals, and almost as many were skin-test-sensitive to pollens. The history of the second episode gave no indication that the positive skin tests had anything to do with the cause of that second episode. Asthmatic bronchitis was the diagnosis in five patients

when the asthma occurred only at the time of new colds, in the presence of a mild degree of allergic sensitiveness. In four patients the skin tests were negative, and the diagnosis of extrinsic asthma in the first episode was made by the history, which showed that the asthma cleared when the patient moved to a new home and thereby presumably escaped from a dust in the former residence. The fact that these skin tests were made many years later may explain the negative findings even if it is known that in many cases positive tests can be demonstrated for a long time after clinical sensitiveness has subsided.

TABLE I. THE AGES BETWEEN WHICH EPISODES OCCUR

PATIENT*	EARLY ASTHMA (EXTRINSIC)	INTERVAL	DURATION (YEARS)	LATER ASTHMA (INTRINSIC)
1. M. P.	4-14 Dogs and cats	14-23	9	23-50 Intrinsic
2. E. N.	3-7 Asthmatic bronchitis—pollen	7-28	21	28-60 Recurrent bronchitis
3. J. F.	9-16 Ragweed—animals	16-30	14	30-40 Three infections—still sensitive to cats
4. J. C.	5-12 Asthmatic bronchitis—grasses	12-30	18	30-60 Intrinsic—died coronary
5. R. C.	5-15 Horse asthma	15-31	16	31-60 Infections—60 clear to age 70
6. M. M.	12-25 Moved—dusts	25-35	10	35-52 Infections; obese
7. S. A.	5-12 Asthmatic bronchitis—(tests negative)	12-35	23	35-80 Attacks at long intervals
8. E. G.	7-12 Asthmatic bronchitis—pollens, dusts	12-35	23	35-52 Intrinsic
9. S. D.	19-28 Asthmatic bronchitis—pollens	28-38	10	38-43 Sinus operation; 49-83 intrinsic
10. E. W.	18-28 On a farm (tests negative)	28-38	10	38-50 Obesity—diet; 50 clear to age 62
11. M. M.	4-26 Animals	26-41	15	41-56 Depletion; colds, still sensitive to animals
12. C. E.	17-20 Asthmatic bronchitis—dog	20-41	15	41-43 Bronchitis; 43 clear to age 71, emphysema
13. P. F.	13-18 Animals	18-44	26	44-47 Intrinsic; divorced and clear to age 58; 58-69 occasional attacks after colds
14. A. J.	5-21 Farm	21-45	24	45-63 "Trouble with husband;" 63 clear to age 69
15. P. S.	15-27 Pollens and dust	27-51	24	51-65 Intrinsic; dead of asthma
16. R. G.	20-25 Moved (tests negative)	25-53	28	53-66 Infections; 66 clear to age 80
17. C. D.	5-15 Animals, pollens	15-55	40	55-73 Bronchitis in winter
18. B. B.	8-37 Moved (tests negative)	37-54	17	54-81 Asthma with colds

*Initials underlined are men.

The later asthma in these patients was due mostly to respiratory infection. The words "infection" and "bronchitis" in Table I refer to the cause of asthma; the symptoms included wheezing and dyspnea as well as cough and malaise. The term "intrinsic" is used in six cases, since in them the evidence for infection was not clear; the sputum was not purulent, and leukocyte counts and sedimentation rates were not elevated. The cause of intrinsic asthma is something that the patient caries within himself at all times and in all places, but we still do not know what this something is; this constitutes an important problem. As the table shows, the term "intrinsic" does not always imply a bad prognosis.

The tendency to asthma is inherited, but only eleven of these eighteen patients gave evidence of hay fever or asthma in their families. It is curious that paranasal sinus disease was found in only one patient in this series.

DISCUSSION

Here is substantial evidence that asthma is a constitutional disease which depends upon something more than the exciting cause of the attack. There are plenty of patients who develop isolated attacks of asthma with long intervals of freedom between, but in most of them the exciting cause is always the same. When all the attacks depend upon exposure to dogs or cats, upon a series of respiratory infections, or upon emotional strain, we are tempted to regard "dog asthma" as a disease quite different from "bacterial asthma" and "psychogenic asthma." Finding even a few patients in whom asthma has been excited by two different kinds of causes is very instructive. It changes our thinking about the asthma problem. This new evidence suggests that a more careful study of the early histories of patients who apply for treatment at a later age will reveal more cases like those described in this account.

Up to now the concept of asthma as a constitutional disease has been hard to prove, but there is nothing new about the idea. In his book, published in 1864, Henry Hyde Salter[2] asked four good questions:

> Is organic disease at the root of the asthmatic tendency?
>
> Is organic disease *necessarily* [italics his] present in all cases of asthma?
>
> Is asthma in its essence a systemic or a local affection?
>
> Is there necessarily in asthmatics some constitutional peculiarity inherited, congenital or acquired?

Dr. Salter noted the onset of asthma after whooping cough, bronchitis, or measles as indicating that damage to the bronchial mucous membrane was the cause of the trouble, but then he admitted that in hay asthma and in ipecacuan asthma there is no reason to think of lung injury and he concluded: "I do not see that we can say anything more definite than that (the cause of asthma) consists of the . . . asthmatic idiosyncrasy with which the individual was born." Ninety-four years have passed since Dr. Salter wrote this, and in that time much has been learned about the exciting causes of asthma. The "trigger mechanisms which fire the charge" are understood quite well. In contrast, however, our knowledge of "why the gun is loaded" is little greater than it was in Dr. Salter's day.

What do we know about it?

First of all, what is the problem? The disease that we call asthma is part of a syndrome which includes hay fever (a typical allergic reaction), chronic vasomotor rhinitis (a distressing disorder comparable, perhaps, to "intrinsic asthma") and nasal polypoid pansinusitis (a part of the picture presented by patients with asthma of a severe type). The syndrome includes eczema of the infantile or atopic type, and it also includes urticaria which alternates with asthma in certain patients. It may include dermatitis of the

contact type, even though this has a slightly different mechanism. These symptoms in the lungs, the nose, and the skin often occur at the same time or in sequence in the same patient. An increase in the blood eosinophils may be found. Meanwhile, the process can be reversible temporarily; it may come and go and, in a consideration of the mechanism, that is an important point. Other chronic reversible disorders, such as migraine, colitis, dysmenorrhea, and possibly arthritis and peptic ulcer, may be related, but they are rarely associated with asthma.

What is the physiologic change that can be initiated sometimes by an allergic reaction, at other times by an infectious process, or at still other times by a psychic disturbance? What produces swelling of the mucous membrane with stimulation of mucous glands, spasm of smooth muscles, and capillary dilatation and leakage in the involved area? The observations of Irwin and associates[3] on the blood vessels of the guinea pig lung in anaphylaxis show that vascular arterial disturbances belong in the picture and suggest a basis for the development of frank periarteritis nodosa in the advanced stages of asthma.

Histamine can produce all of these physiologic changes, and histamine is an effector substance which is readily produced when its precursor (histidine) is acted upon by the enzyme decarboxylase. Present theory says that the symptoms of hay fever, asthma, and eczema result from contact of the allergen with the antibody. This contact takes place on the surface of the cell. The reaction injures the cell and histamine is released. This same mechanism follows other injuries; it occurs in normal persons, as Sir Thomas Lewis[4] could show. Whether or not this release of histamine is abnormal in asthma is still doubtful.

There are secondary questions: First, is histamine produced in excessive quantity? Rose[5] found some increase of histamine in the blood in the early stages of an asthmatic attack, but the concentration fell off rapidly. Serafini,[6] measuring the blood histamine at intervals of a minute or two after a series of positive skin tests in a patient with horse asthma, found a transient rise. Also, the asthmatic patient showed a rise in the blood histamine level after exercise.

Second, is the removal (metabolism) of histamine normal in asthma? There is no clear answer as yet, but a study of end products like indoleacetic acid would be interesting.

Third, is the patient overreactive to histamine? Almost thirty years ago Weiss, Robb, and Blumgart,[7] in a study of blood circulation time, showed that patients with asthma reacted more than normally to the intravenous infusion of dilute histamine. Rackemann, Simon, and Scully[8] found that skin tests made with serial dilutions of histamine gave slightly larger reactions in asthma than in the normal state, but the differences were not impressive.

Whereas histamine plays a part in asthma, its release is not at the beginning of the mechanism. It is easy to put the cart before the horse. Histamine

is a result and not a cause of the antigen-antibody reaction. Meanwhile, the actions of other effectors, such as acetylcholine and serotonin have been considered but with no good evidence so far that they are important in asthma.

The real difference between the asthmatic patient and the normal person depends upon the capacity to develop sensitiveness and perhaps also upon a low resistance to respiratory infections. It is a disorder of the mechanism of immunity which makes the constitutional disease.

One can postulate that in allergic patients the antibodies remain fixed on the cell surface to attract the antigen and produce the symptoms, whereas in normal persons, these antibodies are liberated to the blood stream to produce immunity. If this is a sound theory, it raises questions concerning the formation and the nature of antibodies and the mechanisms by which they are retained on the cell or released to be distributed through the body.

The use of bacterial vaccines and of tuberculin in the treatment of asthma causes reactions and effects which are nonspecific. The effects are beneficial in enough of our patients to require serious attention to the mechanism of their action. So far, very little is known about this mechanism.

New investigations of the immune process point to the nature of gamma globulin; they also point to complement as an essential factor. (See the excellent review by Waksman.[9]) If these studies were applied to asthma, would they reveal a deficiency of one or another of the elements in complement? The studies of the properdin system by Pillemer and colleagues[10] are aimed in the right direction. The investigation of the basic problems of allergy and asthma might be more effective if the approach were made from a new direction.

There are two difficulties with the concept of a chemical disorder: First, our patients can recover from asthma even of severe grade; that shows that whatever chemical change is present must be reversible, at least in part. Second, psychogenic factors are hard to correlate until one appreciates that many chemical processes are under nervous control.

As Professor A. Baird Hastings remarked to me, the problems concerned with immunity are some of the most difficult in biochemistry. To find the active groups in complex proteins is always a challenge, but to find that clinical observation may offer a new approach is stimulating to everybody.

SUMMARY

By demonstrating that the patient can have two distinct episodes of asthma, excited by two different causes, one can conclude that the exciting cause is not the basic cause of the disease. The basis of asthma is a constitutional disease. Whereas studies of histamine have been pursued vigorously, one must recognize that the release of histamine is a result of the antigen-antibody reaction and not a cause of it. The basic differences between the asthmatic patient and the normal person depend upon disturbances of the mechanisms of immunity. In the asthmatic patient the antibodies are fixed to the cells to produce the reactions of allergy; in the normal person they are free in the blood stream to

produce immunity. What it is that controls this difference constitutes a problem of primary importance. The direction of our thinking with respect to the asthma problem can be changed to advantage.

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HYPERSENSITIVITY FOLLOWING INGESTION OF HYDROXYZINE (ATARAX) IN A MEPROBAMATE-SENSITIVE PATIENT

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UNTOWARD reactions to meprobamate are being reported with increasing frequency,[1-7] but in a review of the literature we were unable to find a single case of severe hypersensitive reaction to hydroxyzine hydrochloride. In fact, the side effects from this drug have been reported as infrequent and mild,[8] and the Council on Pharmacy and Chemistry of the American Medical Association has reported the drug as having a low toxicity.[9]

CASE REPORT

A 39-year-old man, while apparently recovering from a dermatosis caused by meprobamate, received hydroxyzine as substitute therapy and experienced an acute serumlike reaction shortly thereafter. He had taken meprobamate without incident from 1956 until July, 1957. The drug was discontinued thereafter until Sept. 10, 1957, when he resumed his usual dose of 400 mg. three times daily. The medication was again stopped on Sept. 15, 1957, because of the appearance of a macular erythematous discrete rash which was said to have extended over the entire body. The patient was seen on Sept. 16, 1957, complaining of a mild sore throat. The pharynx was injected, and Erythrocin was prescribed for the infection. At this time a slight macular rash but no angioedema was noted, and 25 mg. tablets of hydroxyzine were prescribed as a substitute for the meprobamate. The patient did not take the hydroxyzine until the early morning of Sept. 18, 1957, following which he stated that a slight macular nonpruritic rash was noted. The second dose was taken four hours later and was followed shortly thereafter by tightness in the chest, difficult breathing, and later a generalized rash and swelling of the face, feet, and hands. He was admitted to the hospital and immediately was given 0.5 c.c. of epinephrine subcutaneously, and an intravenous infusion of 5 per cent glucose containing 25 mg. of ACTH was started. Benadryl, 50 mg. four times daily, and chloral hydrate at bedtime and as needed were ordered.

The admission temperature was 101° F.; the pulse was 100; and the blood pressure was 115/70. Aside from marked dyspnea, a bright red rash over the entire body, angioedema, and painful arthralgia of the wrists and ankles, the physical examination was not remarkable. The blood count showed white blood cells, 14,900; neutrophils, 82; monocytes, 3; lymphocytes, 15; hemoglobin, 14.5 grams; and hematocrit, 50 volume per cent. The urine gravity was 1.020; microscopically, 4 to 7 red blood cells and 0 to 4 white blood cells per high-power field and occasional granular casts were reported. The nonprotein nitrogen was 26.66 mg., and the cephalin flocculation at the end of forty-eight hours was reported as 3 plus. Only one additional injection of epinephrine was required for relief of the dyspnea some twelve hours after the initial dose.

On the second day of hospitalization the rash appeared maculopapular; the skin of the inner thighs and scrotum was a bright magenta color and itched intensely. Despite the low-grade fever, starch baths followed by application of oil emulsion were ordered. The intravenous infusion of ACTH in glucose was repeated.

The patient showed progressive improvement and was discharged from the hospital on the fourth day after admission. Subsequently there was no return of his symptoms.

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There was no personal history of allergy except for a migraine syndrome, and the only suggestion of an allergic family history was that a brother was said to have migraine and a grandfather had eczema.

Apparently the patient had not had any previous episodes of drug sensitivity, although a review of his record (available to 1950) showed that he had received a number of drugs with sensitizing potentiality. These drugs included barbital, Dilantin, salicylates, Syntropan, codeine, amphetamine, aspirin, belladonna, ergotamine tartrate, phenacetin, nicotinic acid, Co-Elorine, and salicylamide.

COMMENT

The advent of the so-called tranquilizing agents has not only begun a new era in psychopharmacology but likewise has introduced a group of drugs which may pose problems for the dermato-allergist and others interested in these pharmaceutics.

It is hardly surprising that instances of untoward reaction to meprobamate had been reported, considering the popularity of the drug and the quantity which is being used. However, it was not thought that meprobamate had great sensitizing possibilities. Berger[10] stated: "It is not to be expected that a compound of such simple aliphatic structure without either ring structures or unsaturated linkages will induce hypersensitizations as often as more complex compounds."

Berger[11] divides the more important tranquilizers into four groups:

1. Compounds derived from phenothiazine, the more popular being chlorpromazine (Thorazine), promazine (Sparine), mepazine (Pacatal), procloperazine (Compazine), and NP-207 (Kinross-Wright, 1956). Likewise in this group are the antihistamine, promethazine (Phenergan); phenothiazine, an anthelmintic largely discarded because it sometimes caused blood dyscrasias and toxic hepatitis; and the antiparkinsonian agents, diethazine (Dipareol) and ethopropazine (Parsidol).

2. Reserpine and related alkaloids, such as deserpidine and rescinnamine.

3. Compounds derived from diphenylmethane: azacyclonal (Frenquel), benactyzine (Suavitil), and hydroxyzine (Atarax). Likewise closely related are the antispasmodic adiphenine (Trasentine); the antiemetic, meclizine (Bonamine); and the antihistaminic, chlorcyclizine (Perazil).

4. Compounds derived from substitute propanediols, such as meprobamate (Equanil and Miltown), mephenesin (Tolserol and Mephate), and 2-substituted, 4-hydroxymethyl, 1,3-dioxolanes, such as Glyketal and Dimethylane.

In view of the reports[8, 9, 12] of the almost complete absence of toxic or hypersensitive reaction to hydroxyzine, it is with some trepidation that we present this case which suggests such probability. The possibility that this patient's anaphylactic-like reaction following the ingestion of hydroxyzine represented a delayed serum type of reaction to a meprobamate hapten does not seem likely. The possibility that meprobamate, although not chemically closely related, could sensitize a patient to hydroxyzine is to be considered.

The desirability that this patient again be given hydroxyzine to determine whether or not sensitivity to the drug is present is recognized. So far we have been unable to gain his consent to take even a small amount of the drug under controlled conditions.

It is to be hoped that after a more prolonged, repeated, and generally greater quantitative experience with hydroxyzine the present opinion of the relative freedom from toxicity or antigencity of the drug may be preserved.

SUMMARY

A case of apparent hypersensitivity to hydroxyzine hydrochloride (Atarax) in a 39-year-old white man known to be allergic to meprobamate is presented. The patient had shown no previous allergic manifestations, although he did suffer from migraine, as did one of his brothers, and his grandfather was said to have had eczema.

Meprobamate and hydroxyzine are not closely related chemically, but the possibility of related sensitizing properties is considered. No cases of hypersensitivity to hydroxyzine have been previously reported, and the drug has been considered relatively free from toxic or antigenic properties.

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STUDIES IN ALLERGY

I. Serotonin, Histamine, and Antigen-Antibody Complex Activity in Isolated Sensitized Guinea Pig Uteri

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DURING the second decade of the twentieth century, Schultz[1] and Dale[2] developed a method for assaying reactivity of smooth-muscle preparations to foreign proteins and antigens in vitro. Since that time the sensitized guinea pig uterus and ileum have been used extensively for the study of allergenic sensitization and the basic physiology of anaphylaxis and allergic reactions.[3-6]

The Schultz-Dale apparatus and technique were further developed by Coulson and co-workers,[7] who have shown the great specificity and sensitivity of this reaction in detecting antigens of the order of 0.05 meg. of ovalbumin. This sensitivity is 20 to 200 times that of the precipitin test and much greater than gross anaphylactic shock and anaphylactic sensitization.

For these reasons, it was felt that the Schultz-Dale reaction would be useful in studying blocking antibodies to specific antigens which would prevent the anaphylactic reaction of sensitized guinea pig uterine muscle cells to specific antigens.

METHOD

Twenty-five virgin female guinea pigs, each weighing 300 grams, were sensitized by the injection of 1.0 mg. protein per 100 grams body weight of alum-precipitated protein antigen, egg albumin, ragweed, house dust, and feathers prepared by the method of Coulson and Stevens.[8] After a three-week incubation period the animals were sacrificed at weekly intervals by a blow on the head or by anaphylactic shock produced with antigen injected intracardially. This allowed ample time for full sensitization to develop and for adequate testing of the uterine muscles. The uteri were removed and tested in an oxygen-aerated muscle bath with a perfusion bath volume of 25 ml. at a standard room temperature of 25° C. The bath contained a low-calcium Tyrode solution recommended by Coulson,[7] the formula of which follows:

NaCl	8.0 Gm.	$NaHCO_3$	1.0 Gm.
KCl	0.2 Gm.	NaH_2PO_4	0.05 Gm.
$CaCl_2$	0.05 Gm.	Glucose	1.0 Gm.
$MgCl_2$	0.10 Gm.	Water to make	1,000 ml.

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The foregoing experimental conditions were used because of the recommendation by Dalgliesh and colleagues[9] that they reduce the spontaneous activity of smooth muscle.

The uterine muscle segments were suspended in the bath, allowed to come to a base line, and then subjected to various antigens, antigen-serum mixtures, and other test compounds, such as histamine, serotonin, and acetylcholine. The resulting contractions were recorded on a kymograph rotated at 0.492 cm. per minute.

The antigens were obtained from commercial sources (egg albumin)* and the Aspenwall VA Hospital Allergy Service† at Pittsburgh, Pennsylvania. The sera for the antigen-sera mixtures were obtained from allergy patients seen in the outpatient service and in the wards of the medical service of the VA Hospital in Omaha.‡ Blood was drawn while patients were on hyposensitization treatment. Guinea pig serum was obtained by cardiac puncture from animals sensitized by subcutaneously injected alum-precipitated antigens.

Antigen-antibody complexes were formed by mixing an appropriate amount of antigenic protein (egg albumin, ragweed, house dust, and feathers) in a ratio of 1 to 100 with dialyzed human or guinea pig serum protein. These mixtures were incubated for thirty minutes at 37° C. and then for twenty-four hours at 4° C. Following this, the mixtures were centrifuged, and the supernatant was used for testing in the muscle bath.

An operation was devised whereby one uterine horn was removed from the sensitized guinea pig under ether anesthesia and the abdomen was sutured after hemostasis of the uterine stump. Two or three hours later the animal was anesthetized again and blood was drawn by cardiac puncture. Through the same intracardiac needle, 3 mg. of the appropriate antigen (egg albumin, house dust, ragweed, or feathers) was given. This was generally followed by an anaphylactic reaction. After death, the remaining uterus was removed and placed in the Schultz-Dale apparatus for testing. The uterine horn removed prior to antigenic shocking is called the preshock horn, and that removed after antigenic shocking is termed the postshock horn.

Routinely, each strip was tested for its reactivity to acetylcholine base§ (32 mcg. per milliliter), histamine base‖ (0.2 mcg. per milliliter), and serotonin base¶ (7 mcg. per milliliter). Depending upon the antigen or antigens used in sensitization, the strips were next tested with saline solutions of ovalbumin (EA), 4 mcg. P per milliliter; ragweed protein (RW) 16 mcg. PN per milliliter; house dust protein (HD), 18 mcg. PN per milliliter; and feathers protein 7 mcg. P per milliliter. After the antigen testing the strips were again

*Soluble egg albumin (Difco).

†Ragweed, house dust, and feather extract were kindly supplied by Dr. L. H. Criep, Aspenwall VA Hospital, Pittsburgh, Pennsylvania.

‡Sera supplied through the interest and kindness of Dr. Morris H. Brodky, Omaha VA Hospital Outpatient Service.

§Acetylcholine chloride (Nutritional Biochemicals Corp.).

‖Histamine diphosphate (Abbott).

¶Serotonin creatinine sulfate (California Research Foundation).

subjected to histamine, serotonin, and acetylcholine, respectively. Between each two test situations, the bath and strip were washed with several aliquots of 25 ml. of Tyrode solution.

A contraction was considered a significant response if it exceeded twice the height of the spontaneous contraction, if present, or was at least the same height as that produced by histamine base (0.2 mcg. per milliliter).

The use of a low-calcium Tyrode solution at 25° C. was found to be most satisfactory in producing a constant base line with a minimum of spontaneous contraction. We have found the uterine muscle of the guinea pig to be exceptionally responsive to acetylcholine and histamine but minimally responsive to serotonin in dosages approximating 300 to 400 times that needed for the rat and mouse uterus. With histamine, adequate responses are obtained with 5 mcg. per 25 ml. or 0.2 mcg. per milliliter. These are substantially less than those reported by Coulson (100 mcg. per 50 ml. or 2.0 mcg. per milliliter). Since we were not interested in the quantitative titration of the antigen reaction and since a preliminary pilot study showed that maximal consistent responses occurred with protein levels of the order of 4 mcg. egg albumin P per milliliter, 16 mcg. ragweed PN per milliliter, 18 mcg. house dust PN per milliliter, 7 mcg. feathers P per milliliter, these were used throughout the experiments in order to provide comparable contractions. All guinea pigs were sensitized with alum-precipitated proteins[7, 8] to ensure maximum sensitivity and to eliminate false negative reactions.

RESULTS

Fig. 1 shows the type of responses which were registered on the kymograph of the Schultz-Dale apparatus as a result of the contractions and relaxations of the guinea pig uterine strips. The upper half of the figure shows a typical pattern obtained from a normal untreated guinea pig uterine muscle strip. The normal strip responds repeatedly to acetylcholine and to histamine, but infrequently (30 per cent) to serotonin. The normal horn does not respond to such antigens as ragweed, house dust, feather extracts, and egg albumin. Fig. 1 (lower half) and Fig. 2 (upper experiment) show typical patterns obtained from sensitized horns. Here the responses are usually the same as those of the normal tissues, except that response is obtained from the antigen or antigens with which the animal had been sensitized.

In the case of the shocked pig the situation is quite different. As is shown in Fig. 2 (lower experiment), where the guinea pig had been sensitized and then shocked with feather extract, the strip responded to acetylcholine and histamine and also responded markedly to serotonin. The uterine horn segment did not respond to feathers because of previous desensitization by antigenic shocking.

In several experiments we were able to show that a soluble antigen-antibody complex produces not only a higher percentage of responses in sensitized guinea-pig uteri but also a greater contraction of uterine strips than does the antigen alone. Fig. 3 shows two strips taken from the same sensitized

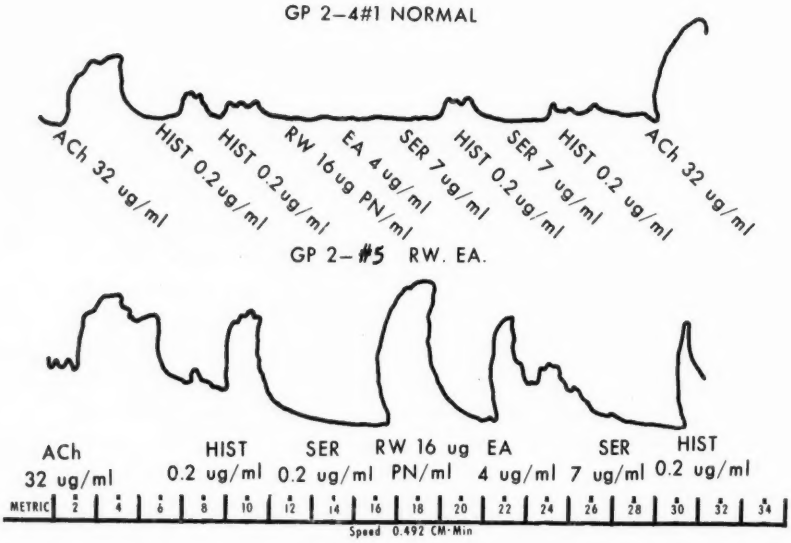

Fig. 1.—*Upper half:* Responses of a normal guinea pig uterine strip to various test substances.

Lower half: Responses of a guinea pig uterine strip sensitized to ragweed and egg albumin antigens.

Metric scale in centimeters. One minute equivalent to 0.492 cm.

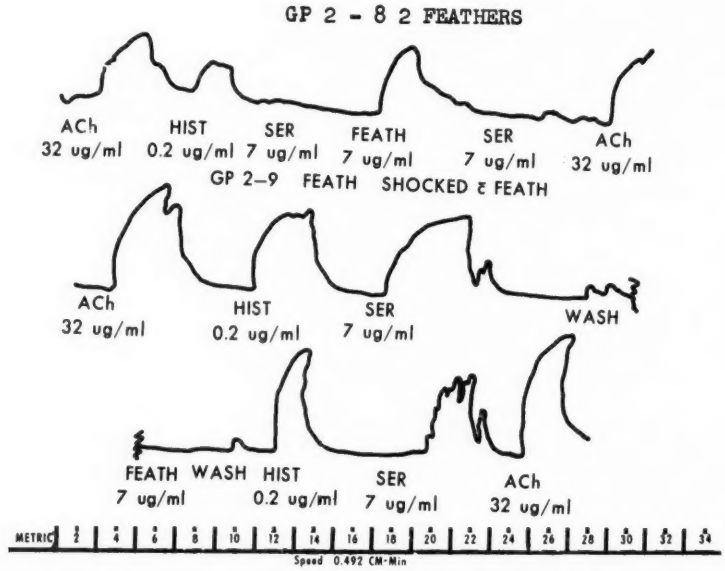

Fig. 2.—*Upper experiment:* Responses of a guinea pig uterine strip sensitized to feather antigen.

Lower experiment: Responses of a uterine strip taken from a guinea pig sensitized with feather antigen and shocked with feathers.

animal (HD). Both muscles responded equally to the same amount of histamine. When house dust (450 meg. PN) was mixed with saline-dialyzed serum protein (in a ratio of 1:100) from a patient who had been on a hyposensitization regimen and this mixture was added to the 25 ml. bath, the response obtained was much greater than that obtained from the other strip treated with the antigen alone.

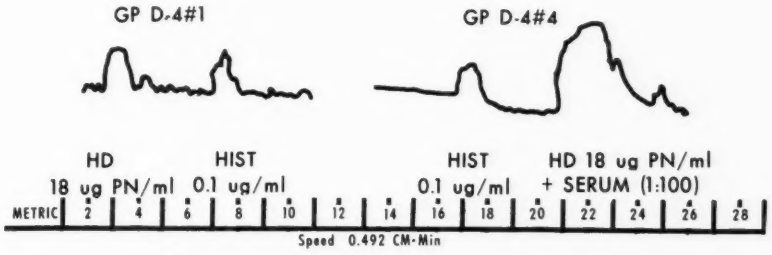

Fig. 3.—Responses of uterine strips taken from the same guinea pig sensitized with house dust antigen. First pattern shows response to antigen alone. Second pattern shows increased response to antigen-antibody complex.

Table I summarizes the results of the present study. Eighty per cent of normal, nonsensitized uterine horns responded to histamine. Following allergenic sensitization, 66 per cent of the sensitized uterine horn strips responded to histamine. The observed decrease in the number of horns reacting to histamine after sensitization was significant at the 0.05 level of probability. Histamine reactivity of the preshock sensitized uterine horn was not different from the histamine reactivity of the postshock sensitized horn after in vivo antigen shocking.

TABLE I. RESPONSE OF VIRGIN GUINEA PIG UTERI TO ANTIGENIC SHOCKING

NO. SEGMENTS TESTED	RESPONSE ANTIGEN	RESPONSE TO ANTIGEN AND SERUM COMPLEX	SEROTONIN RESPONSE	HISTAMINE RESPONSE
13 normal nonsensitized horn segments	0%	0%	30%[a]	80%[a]
108 sensitized preshock horn segments	(a) RW = 52% (b) EA = 59% (c) HD = 29% (d) F. = 60%	RW = 87% EA = 78% HD = 65%	41%[b] 21 of 51	66%[b] 72 of 108
69 sensitized postshock horn segments			61%[c] 25 of 41	66%[c] 46 of 69
Chi-square tests	(a) RW – RW + serum $P > .01$ (b) EA – EA + serum $P > .01$ (c) HD – HD + serum $P > .01$		(a-b) $P > 0.10$ (a-c) $P > 0.01$ (b-c) $P > 0.01$	(a-b) $P > 0.05$ (a-c) $P > 0.20$ (b-c) $P > 1.00$

Thirty per cent of normal uterine horns were sensitive to serotonin. After allergenic sensitization, 41 per cent of the sensitized uterine horns were sensitive to serotonin. This difference is not significant at the 0.10 level. When

the uterine muscle strips were subjected to in vivo anaphylaxis, the sensitivity to serotonin increased to 61 per cent positive responses, which was significant at the 0.01 level. Normal control uteri showed unchanged responses to serotonin in all cases when treated with antigen in the Coulson low-calcium Tyrode bath. Sensitized uterine muscles responded to ragweed protein 52 per cent, egg albumin 59 per cent, house dust protein 29 per cent, and feathers 60 per cent, demonstrating the relative activity of these proteins and protein mixtures as antigens and anaphylactogens. When ragweed protein was incubated with the dialyzed sera of patients undergoing hyposensitization to ragweed and this complex was added to the solution bathing the sensitized muscle, the positive response increased to 87 per cent. This increase was significant at the 0.01 level. Egg albumin mixed with sensitized guinea pig sera showed response increased to 78 per cent. This was significant at the 0.01 level. Similarly, when house dust protein was incubated with dialyzed sera of patients and added to the sensitized uterine muscle bath, the percentage of positive responses rose to 65 per cent. This rise was significant at the 0.01 level. Sera of patients under hyposensitization regimens alone showed only slight reactions on sensitized or unsensitized guinea pig uteri, and these were diminished or removed by dialysis of the sera.

Anaphylactic shocking by ragweed, egg albumin, feather, and house dust antigens resulted in increased serotonin sensitivity in guinea pig uteri. A significant reduction was noted in histamine sensitivity. This finding suggested that anaphylaxis may be a more complex phenomenon than previously postulated. Increased serotonin sensitivity at the shock-organ cell level may play a role in the production of anaphylaxis.

Antigen-antibody complexes formed by admixture of hyposensitized sera and antigen produce a greater incidence of positive anaphylactic reactions in sensitized guinea pig uteri than antigens alone. This may confirm published works of other authors concerning antigen-antibody complexes.[6, 10, 11]

No evidence was found in this study for the presence of blocking antibodies which protect sensitized uteri against antigens, either in human hyposensitized blood or in the blood of guinea pigs sensitized by alum-precipitated antigens.

DISCUSSION

We were puzzled by the lack of blocking activity exhibited by hyposensitized sera. Instead, we noted that anaphylactic reactions in sensitized uteri were markedly enhanced by addition to the muscle bath of mixtures of hyposensitized human sera and specific antigen. The human sera had been dialyzed against normal saline solution to remove histamine, serotonin, and other uterine muscle stimulants. Our conclusion is that the antigen-antibody complex acted directly upon the mediating system in the uterine muscle or nerve plexus to produce the anaphylactic contraction. The lack of species specificity for this reaction was demonstrated by the finding of a similar reaction produced by guinea pig sera and egg albumin against uteri sensitized to egg albumin. No evidence of antigenic blocking was found.

Can anaphylaxis be a result of increased sensitivity of the uterus to serotonin or histamine? Our study of histamine reactions showed that histamine response was significantly decreased by sensitization, and therefore anaphylaxis cannot be considered to be mediated by histamine alone. Uterine sensitivity to serotonin is not changed significantly by sensitization of the uteri, and an increased level of serotonin in the tissue is not presumed to be the factor responsible for this increased contraction rate and intensity. Fink and Gardner[4] were unable to demonstrate mediation of anaphylactic contractions by serotonin alone in guinea pig uteri. At this time the best explanation is that advanced by Germuth and McKinnon,[6] namely, that the shocking property of antigen-antibody mixtures is due to the presence of soluble antigen-antibody complexes. They suggest that anaphylactic shock does not require actual interaction of antigen-antibody complexes in the tissues but may be produced by preformed antigen-antibody complexes acting on susceptible cells.

Serotonin sensitivity is markedly and significantly increased by in vivo shocking with antigen. This is true for any antigen used in this series. Weissbach and associates[12] and Fink and Gardner[4] demonstrated decreased serotonin levels in guinea pig lungs and lung perfusates after shocking by antigen. These findings have led us to consider that anaphylactic responses in the guinea pig uterus at least may be produced by a more complex reaction than previously hypothesized. Anaphylaxis may involve the action of higher concentrations of serotonin released from platelets[13, 14] upon a tissue whose sensitivity to serotonin has been greatly altered by the in vivo anaphylactic reaction due to soluble antigen-antibody complex. Histamine sensitivity, though not significantly changed by anaphylaxis, may act to enhance or perhaps synergize serotonin reaction at the tissue level. One anaphylactic reaction to antigen or antigen-antibody complex blocks further response to the same antigen.

SUMMARY

The uteri of twenty-five virgin allergen-sensitized guinea pigs were studied in the Schultz-Dale muscle bath apparatus before and after in vitro and in vivo shocking. All uterine horns from guinea pigs responded to acetylcholine. Eighty-two per cent of normal nonsensitized horns contracted on addition of histamine. After sensitization, 61 per cent of the sensitized horns responded to histamine. Thirty to forty per cent of the uterine horns responded to serotonin before and after sensitization. After shocking by in vivo antigenic exposure, 61 per cent of the uteri responded maximally to serotonin. A significant increase in response of sensitized uteri was obtained through the use of soluble antigen-antibody complexes over the use of antigen alone.

Illustrations were prepared by Frank A. Roberts and John E. Friel, Medical Illustration Service, VA Hospital, Omaha, Nebraska.

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Editorial

THE TUBERCULIN, THE ARTHUS, AND THE ATOPIC ALLERGIC RESPONSES

IT WAS pointed out more than twenty-five years ago[1] that the injection into tuberculous guinea pigs of egg white, or more especially ovoglobulin, is followed by two types of allergic state which develop in sequence. The first is the tuberculin type, a delayed tissue reaction apparently not mediated by circulating antibody. Sooner or later, depending on the experimental procedure, the delayed type of response gives way to the familiar susceptibility to anaphylactic shock and the Arthus type of tissue response. These last are associated with, and apparently mediated by, precipitating antiobdy having all the characteristic of γ globulin. So striking is this second response that in most of the research and writings it has tended to eclipse the first. However, widespread interest in the tuberculin type of allergy was aroused by the demonstration that white cells obtained from tuberculous guinea pigs would confer a transient allergy of the tuberculin type when injected in quantity into normal animals.[2] This phenomenon has proved to be more easily demonstrable in man than in the guinea pig, and it can be achieved with a number of different allergens. As a cursory perusal of the current issues of a single journal[3] will show, the tuberculin type of allergic response and its relationship to the Arthus or anaphylactic type are now receiving increasing attention.

The prevailing view today is essentially that proposed twenty-five years ago, namely, that the tuberculin type of allergy is the initial (more primitive?) response and is superseded (depending on the antigen and adjuvant used, the quantity injected, and the route of injection) by the Arthus type which is associated with circulating antibody. Recent evidence suggests that in tissue culture this circulating antibody can protect cells endowed with the tuberculin type of allergy from the damage which, as was also shown over twenty-five years ago,[4] follows exposure to the appropriate antigen. If this is, indeed, the case, the tuberculin type of allergy might persist undetected after the Arthus type develops. It is relevant to point out in this connection that interpretation of the observed coexistence of the two types of response in some of the early experiments[1 (b)] was rendered difficult by the complex nautre of the antigen used (namely, unfractionated egg white), since it had been shown[1 (a)] that under the experimental conditions ovoglobulin favored the development of the delayed type of response, whereas ovalbumin favored the Arthus type.

As a relationship emerges between the tuberculin and the Arthus types of allergic response, one is increasingly tempted to ask where the atopic allergic response and the skin-sensitizing antibody belong in the immunologic scheme of things. The common view is that the atopic response simulates the Arthus response more closely than the tuberculin type in that antibody is cast off in quantity into the extracellular fluids and the allergic response is a prompt one. The atopic antibody has peculiarities of its own, however, which set it off from the precipitating antibodies characterizing the Arthus type. Though often to be found free in the blood, the atopic antibody has not been shown conclusively to react with the appropriate allergen (antigen) *in vitro*, and its presence becomes evident only after it has become fixed to tissue. Furthermore, tissue sensitized by this antibody can be "protected" by the so-called neutralizing or blocking antibody. Since in both the tuberculin and the atopic types of response demonstrable reactions occur only at the cellular level, and since in both types a circulating antibody can be induced which appears to "protect," these two types of allergic response may be more closely related than the striking differences in their manifestations would suggest.

F. C. L.

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Announcements

Oregon Society of Allergy

The new president of the Oregon Society of Allergy, elected at the annual meeting in Portland on Sept. 3, 1958, is Dr. Nicholas P. Sullivan of Eugene. Dr. Robert L. Cutter, Bend, was elected vice-president, and Dr. Alvin D. Wert, Portland, was named secretary-treasurer. Dr. Roy R. Matteri of Portland is retiring president.

The Society has announced a Workshop in Allergy to be held in Portland on Friday, October 24, at the Medical Dental Building Auditorium. Guest speaker will be Lawrence J. Halpin, M.D., of Cedar Rapids, Iowa.

Mid-West Forum on Allergy

The Mid-West Forum on Allergy will hold its annual meeting on Dec. 6 and 7, 1958, at the Sheraton-Cadillac Hotel, Detroit, Michigan. This meeting of the Forum is sponsored by the Michigan Allergy Society.

For further information, please write to John M. Sheldon, M.D., General Chairman, in care of the University Hospital, Ann Arbor, Michigan.

Mary Putnam Jacobi Fellowship

The Women's Medical Association of the City of New York offers the Mary Putnam Jacobi Fellowship to a graduate woman physician, either American or foreign. This Fellowship will start Oct. 1, 1959, and will amount to $2,000.00, $1,000.00 being available Oct. 1, 1959. The recipient of the Fellowship will be expected to make a report to the committee at the end of the fourth month, following which the second $1,000.00 will be awarded subject to the approval of the committee. The Fellowship is given for medical research, clinical investigation, or postgraduate study in a special field of medicine. The recipient is expected to devote full time to the Fellowship, but exception may be made by the committee under special circumstances.

Application forms for this Fellowship may be obtained from the secretary of the committee after Aug. 1, 1958, and must be returned before Feb. 1, 1959, with the following information: (1) curriculum vitae, (2) a statement from a physician of a recent physical examination, (3) transcripts of college and medical school records, (4) personal letters of recommendation from two or more physicians under whom the applicant has studied, (5) a statement by the applicant as to the problems that she proposes to investigate or the study that she plans to undertake, (6) a statement from the person under whom she proposes to study of his or her interest in her subject, and (7) a recent photograph. All of the above data must be at hand before the application will be considered.

Successful candidates will be notified not later than May 1, 1959.

Ada Chree Reid, M.D., Secretary
118 Riverside Dr.
New York 24, New York

Betty Bacharach Home

The Betty Bacharach Home, in association with the pediatric, medical and psychiatric departments of the Jefferson Medical Center, has organized a unit for the treatment of intractable asthma in children. Children with perennial asthma of more than one year's duration, who are refractory to hyposensitization and other forms of medical treatment, are eligible for admission.

The Betty Bacharach Home is ideally suited for this project. The asthmatic unit is a separate entity. Environmental control is excellent and all facilities, including schooling, are available within the institution. Absecon Island, on which the home is located, is a relatively pollen-free area.

Children from 5 to 15 years of age will be considered for admission. The Betty Bacharach Home will underwrite the cost for all children admitted to the unit. For further information, contact Mr. Simon Lippman, Executive Secretary of the Betty Bacharach Home, Atlantic City, New Jersey.

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